THE AMERICAN JOURNAL OF PATHOLOGY

VOLUME V NOVEMBER, 1929 NUMBER 6

THE FINER HISTOLOGY OF THE NORMAL GLOMERULUS*

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INTRODUCTION

The object of this paper is to review the literature and to present some new facts regarding the histology of the normal human renal glomerulus.

I. REVIEW OF LITERATURE

Bowman's Capsule: In 1688 Malpighi discovered the renal glomerulus by means of injections through the renal artery. He considered it a gland which might possibly give origin to the uriniferous tubule. Schumlansky, 1782, suggested in a diagram some connection between glomeruli and tubules. Littre, 1705, and Johannes Müller, 1830, were the first to describe the capsule. Huschke, 1828, and Müller believed the capsule to be closed except where the vessels entered. Bowman, 1842, proved the union of tubule and glomerulus by a method of successive injection of saturated solutions of potassium bichromate and lead acetate. In both human and animal kidneys the precipitate which formed in the vessels often burst through the glomerular tuft and passed down the tubule. He described the capsule as consisting of an external tunic of transparent homogeneous tissue lined by epithelium. These epithelial cells were non-ciliated, flat and continuous with those of the convoluted tubules. These findings were confirmed in 1845 by Bidder who also noted the continuity of the capsular and tubular basement mem-

* Read before The American Association of Pathologists and Bacteriologists, Chicago, Ill., March 29, 1929.

Received for publication July 20, 1929.

branes. Roth, 1864, and His, 1865, were the first to demonstrate cell boundaries with silver preparations. Ludwig, 1872, described the capsule as consisting of "a mosaic of cells closely resembling those composing the wall of the blood and lymphatic capillaries with a little connective tissue around the outer surface." Drasch, 1877, saw that the nuclei of adjacent cells lay side by side in eccentric positions. Herring, 1900, after a comprehensive review of the embryology of the kidney, concluded that the cavity of Bowman's capsule should be regarded as a body cavity, especially differentiated for urinary secretion.

Mall, 1896, showed the capsular basement membrane to be composed of longitudinally and circularly disposed reticular fibrils, which when very dense and compressed, gave a homogeneous appearance. They anastomosed with the fibrils of adjacent tubules. In spite of these facts, von Ebner in 1902 described the membrane as structureless and glassy. In 1902 Mall was able to show that there were two basal membranes, an inner one homogeneous and structureless, applied to the bases of the epithelial cells, and an outer one interlacing and fibrillar. The latter was part of the reticular stroma of the kidney. Rühle, 1897, Russakoff, 1908, and Corner, 1920, confirmed Mall on these points. Corner believed the fibrillar membrana propria to be produced by the endothelium of adjacent capillaries. von Frisch, 1915, although agreeing that the tubules have a double basement membrane, definitely stated that the capsular membrana propria is a structureless glassy skin. Schäffer, 1927, concluded that the membrane must be considered as a cuticular excretion of the epithelial cells.

Glomerular Endothelium: The history of the cytology of the glomerular tuft begins with Bowman, 1842. He described the vascular loops as lying naked within the lumen of the capsule, held together only by their mutual interlacement. "The Malpighian capillary system stands alone among similar structures in being bare." Among his supporters were Johnson, 1850, Frerichs, 1851, and Henle, 1873. Henle stated: "The vessels in the glomerulus have the calibre of capillaries. Their framework is a structureless wall possessing elliptical nuclei." Many attempts were made to find cell boundaries between these capillary nuclei. Chrzonszczewsky, 1864, Ludwig, 1872, Drasch, 1877, Ribbert, 1879, Hortoles, 1881, and Buday, 1906, after numerous silver injections, were unsuccessful although they

could easily demonstrate boundaries between the endothelial cells of the vas afferens and vas efferens. Langhans, 1879, described the endothelial layer as having very few nuclei. Eliaschoff, 1883, found that these nuclei were more conspicuous in rabbits than in other animals. In 1886, Nussbaum demonstrated cell boundaries in the endothelium of the frog's glomeruli. These cells projected into the lumen and were very distinct in cross-section. von Moellendorff, 1927, described the endothelium of the human glomerulus as a fine layer with a few nuclei and visible cytoplasm only where such nuclei lay. He could not find cell boundaries.

Glomerular Epithelium: The epithelial covering of the glomerular tuft was first described by Gerlach in 1845 and 1848. By injections through the ureter he was able to show that the vascular loops were separated from the capsular space by cells which he believed were the essential elements of a gland. These cells formed a layer over the tips and crevices of the glomerulus. Bidder, 1845, suggested but could not prove conclusively the presence of glomerular epithelium. Carus, 1850, von Wittich, 1851, Koelliker, 1854, McDonnell, 1855, Chrzonszczewsky, 1864, Duncan, 1867, and Toldt, 1874, all supported Gerlach. In 1857 Isaacs injected glomeruli by way of the ureter and tubules until the capsules ruptured. With a dissecting microscope he examined through the hole in the capsule the epithelial covering of the loops. His illustrations showed how much larger these cells were than those lining Bowman's capsule. Moleschott, 1862, measured the glomerular and capsular epithelial cells and found the diameters to average 0.01 and 0.006 mm., respectively. Steudener, 1864, saw a fine covering over the glomerular loops but could not recognize it as epithelium. Schweigger-Seidel, 1865, and Seng, 1871, observed the presence of epithelium over the tips of the loops in the embryo. Ludwig, 1872, saw that the walls of the capillaries were separated from the capsular contents by "a layer of not very well defined cells with spherical nuclei." He was not sure that these were continuous from lobule to lobule. R. Heidenhain, 1874, injected the renal arteries of cats, birds, rats, field mice, rabbits, guinea pigs, sheep, pigs and cows, and found the epithelial cells forming a continuous layer over and between the loops. His work was confirmed by the findings of Frey, 1875, Langhans, 1879, Ribbert, 1879, and Nauwerck, 1884. Ribbert stated that the numerous nuclei observed in a normal glomerulus were for the most

part epithelial. Drasch, 1877, and von Ebner, 1902, believed this epithelium was in the form of a syncytium. Ziegler, 1879, preferred to consider it as endothelium comparable to the lining of the serous cavities. Nussbaum, 1886, clearly distinguished the large glomerular epithelium from the smaller endothelium. He believed the epithelial cells were often multinucleated and that amitosis occurred in them. He recognized the continuity of glomerular and capsular epithelium. Hansemann, 1887, with Isaac's technique isolated the glomerular epithelium and described the cells as flat, often multinucleated, and taller than those lining the capsule. He pointed out the more rapid postmortem digestion of the epithelial than of the endothelial cells. In 1900, Herring's review of the development of the glomerulus explained completely the position and derivation of glomerular epithelium. In a 1909 Harvey lecture, Huber stated that the columnar glomerular epithelium of the embryo became pavement epithelium in the adult. Mertz, 1918, in a quantitative study of the cells in the average 10 micron section of a human glomerulus, was unable to find sufficient morphological difference between endothelium and epithelium to count them separately. Löhlein, 1910, Gross, 1919, Fahr, 1925, Munk, 1925, and Elwyn, 1926, all described glomerular epithelium and its pathological changes. Gross preferred to think of it as a syncytium rather than true epithelium. Fahr stated that glomerular epithelium was so closely related to tubular that it would seem to be secretory. Zimmerman, 1911, 1915 and 1923, demonstrated boundaries between these cells in cats and hedgehogs, but preferred to call them pericytes. von Moellendorff, 1927, described the "deck" cells or glomerular epithelium as morphologically similar to the adventitial cells or pericytes of the capillary bed. He believed these cells have long, branching, anastomosing processes which form a network over the glomerular loops. He ascribed to their mesenchymal origin, their ability to take the form of adventitial cells and to transform into free round cells in pathological conditions. Vimtrup, 1928, adhered to the older conception of an epithelial covering closely applied to the surface of each capillary loop. Volterra, 1928, described these cells as perithelial but did not see any processes on them. He concluded that the cell branches described by von Moellendorff belonged to the glomerular basement membrane and were a part of the connective tissue adventitia of the capillary tuft. Bargmann, 1929, studied the glomeruli of many species and believed

with von Moellendorff that the branching processes belonged to the "deck" cells.

Glomerular Basement Membrane: The possibility of a membrana propria in the glomerular loops was evidently considered by Bowman and rejected for he wrote: "The capsular basement membrane is perforated by the afferent and efferent vessels and is certainly not reflected over them." Seng, 1871, saw and illustrated the presence and continuity of the glomerular and capsular basal membranes. Toldt, 1874, confirmed this finding in both embryonic and adult human glomeruli. Drasch, 1877, after injection of silver nitrate into the glomerular vessels, saw a formation which depended on a porous condition in a membrane. Langhans' illustrations, 1879, show a basement membrane which he described as a very fine doubly-contoured border. Nussbaum, 1886, after studying the embryology of the malpighian body, searched unsuccessfully for a glomerular membrane and concluded that the wall of a glomerulus had only two layers, endothelial and epithelial. Mall, 1896, after boiling kidney tissue in water, digested frozen sections with pancreatin and found a homogeneous striped membrane still present in the glomerular loops. Rühle, 1897, injected a rabbit's kidney with alcohol and was able to see an indistinct membrane in the glomerular loops. Fibers from the capsular basement membrane passed into the glomerular membrane. During digestion with pancreatin the epithelial and endothelial cells disappeared leaving a regularly striped fibrous membrane showing numerous fine pores. This confirmed the work of Drasch. Regaud and Policard, 1903, studying the kidneys of ophidians stained with alum hematoxylin, demonstrated a thin homogeneous membrane separating the endothelium from the synctyial epiglomerular layer. Hueter, 1908, stained the glomerular basement membrane with Ribbert's connective tissue stain. Gross, 1919, found that the membrane took a gray or brown color with Heidenhain's iron hematoxylin. Ohmori, 1921, obtained a very clear differentiation of the membrane with a rein blau-picric acid dye. Hung, 1922, was able to stain it distinctly if the tissue were boiled before fixation and later put through hematoxylin-eosin, Weigert's elastic tissue stain or Mallory's anilin blue. Krauspe, 1922, using Bielschowsky's method found the glomerular wall to consist of homogeneous gray or black membrane lined inside by endothelium and outside by epithelium. He saw the transition into Bowman's base-

ment membrane but could not detect the fine streaking mentioned by Rühle. Schäffer, 1927, noted the presence of the glomerular membrane but did not consider its structure to be fibrillar. von Moellendorff, 1927, demonstrated a homogeneous membrane with Heidenhain's azan-carmine and with his own eosin-methylene blue. Volterra, 1928, described the membrane as a continuous, argyrophil, net-like, reticular adventitia resting on endothelium but not formed by it and adherent to the pericytes. The processes which von Moellendorff assigned to the "deck" cells were, according to Volterra, the connective tissue fibrils of the membrane. Bargmann, 1929, described the glomerular membrane as a deep black or brown granular line when impregnated with silver.

Glomerular Connective Tissue: Key, in 1865, described star-shaped cells which he considered connective tissue between the glomerular loops. Ludwig, 1872, stated that the capillaries of the tuft had an investment of connective tissue. Klebs, 1863, and 1889, thought there were small numbers of such cells in all glomeruli. Toldt, 1874, saw central cells in the crevices of the tuft which were different from the epithelial cells. However, as the glomerulus developed and became spherical these connective tissue elements were no longer visible. In 1880, Waller confirmed Key's finding. In normal cat glomeruli he distinguished epithelium from "connective tissue corpuscles" which were situated between the lobes and stained with logwood after carmine and gelatin injections. He studied the glomeruli as a whole under a dissecting microscope and considered these cells to have a special affinity for vegetable coloring matter. Greenfield, 1880, also believed there were connective tissue cells within the glomerular tuft and Ribbert, 1879, described their nuclei as being small, spindle-shaped, and more intensely stained with carmine than the larger round finely granular epithelial nuclei. Opposing this view were Drasch, 1877, Langhans, 1885, Nauwerck 1886, Nussbaum, 1886, Hansemann, 1887, Orth, 1893, Mertz, 1918, and von Moellendorff, 1927. Nussbaum concluded that the connective tissue which he expected to find, in consideration of the embryological development, must have been resorbed. Herring, 1900, Mallory, 1914, and Vimtrup, 1928, have stated that some connective tissue persists around the hilum probably continuing into the glomerulus to bind the capillaries together.

With regard to the presence of reticulum within the tuft, John-

ston, 1899, believed these fibrils in Bowman's capsule were not reflected over the glomerulus. As the afferent vessel pierced the capsule, fibrils arose which penetrated the glomerulus, passing in all directions between its capillaries. These became less and less numerous as the periphery was approached. Luna, 1920, using the method of Achūcarro–del Río-Hortega, saw an occasional adventitial sheath in the glomerular capillaries. Corner, 1920, decided that the endothelium of the glomerular tuft was never provided with a reticulum. Krauspe, 1922, employing the Bielschowsky–Maresch technique, after a study of 150 human kidneys, could not find *gitterfasern* in the glomerular capillaries. Foot, 1925, decided that no reticulum was seen in the human renal tuft under ordinary circumstances. Allen, 1927, using silver impregnation concluded that occasional glomeruli showed reticulum fibrils in the tuft, usually near the pedicle. A few fibers radiated peripherally with no constant relation to reticulum cells or capillary endothelium. Bargmann, 1929, saw an argyrophil network deep in the capillary wall but he could not say to what it belonged.

Shape and Size of Glomerulus: Vimtrup, 1928, described the human malpighian body as oval with an average diameter of 200 microns as compared with Fahr's figure of 237 microns.

Mertz, 1918, found that the total number of cells in 10 to 15 micron sections through the greatest diameter of normal glomeruli was constant, and at most 145. Of these 3 to 30 were leucocytes, leaving 130 endothelial and epithelial. von Moellendorff, 1927, did not make a quantitative study but concluded that there were at least ten times as many epithelial as endothelial cells. Bargmann, 1929, made the same observation.

Development of the Glomerulus: According to Herring, 1900, and Huber, 1909, the malpighian body, convoluted tubules, Henle's loops, junctional tubules, connective tissue framework and capsule arise from the kidney blastema, a mass of cells formed from the intermediate cell mass. Blood vessels are partly of the same origin and partly branches from the renal artery. Malpighian bodies and their tubules begin to appear at the end of the second month. Each arises as a solid mass of cells which acquires a lumen and becomes S-shaped. The lower limb of the "S" becomes the malpighian body, the upper and middle limbs form the convoluted tubules. The convex side of the lower limb is formed by the epithelium which later lines

Bowman's capsule, the concave side by the epithelium which later covers the glomerulus. The glomerulus is at first non-vascular and is formed by a thickening of the epithelium rather than by an invagination. The capillaries form *in situ* from mesenchymal connective tissue cells close to the base of the glomerulus and are joined by a branch of the renal artery. The division of the glomerulus into lobes is due to the penetration of the epithelial cells between the capillary loops.

Summary

To summarize the present status of the histology of the normal glomerulus, it may be said:

1. The shape is oval and the diameter varies between 200 and 237 microns.

2. The capsule consists of a basement membrane lined by flat epithelial cells which become taller near the opening into the tubule. The structure of the membrane and its relation to the glomerular membrane are not agreed upon.

3. The wall of the glomerular loop contains a basement membrane whose porosity and fibrillar or homogeneous character are unsettled subjects.

4. Within the glomerular membrane are a few endothelial cells between which, boundaries have not been definitely established.

5. Outside the glomerular membrane is a layer of cells whose epithelial, adventitial and syncytial characters are controversial points.

6. The presence of reticular fibrils in the tuft beyond the wall of the vas afferens is indefinite as is also the existence there of connective tissue cells.

II. Methods Used and Results Obtained in this Study

Fixation of Tissues: In general the results were best following Zenker or Helly fixation. However, most of the tissues available for this work had already been fixed in 10 per cent formalin. Davidoff, 1928, described a method of taking nerve tissue from formalin to Zenker. This was tried on kidney tissue and was found to work very successfully. The technique may be applied to the tissue in blocks or to paraffin sections.

(*a*) For paraffin sections of formalin-fixed tissues.

1. One hour in ammonia (40 drops to 10 cc. of water).
2. One hour in running water.
3. One hour in Zenker's or Helly's fluid.
4. One hour in running water.

(*b*) For blocks of formalin-fixed tissue.

1. Two days in paraffin oven at 40° C in ammonia (40 drops to 100 cc. of water).
2. Twenty-four hours in running water.
3. Zenker twelve hours, or Helly five hours.
4. Twelve hours in running water.

Staining of Tissues: The following stains have been used: Hematoxylin and eosin, Mallory's eosin-methylene blue, methyl green-pyronin, Van Gieson, Weigert's elastic tissue stain, Ohmori's rein blau-picric acid, Mallory's anilin blue, Heidenhain's azan-carmine modification of Mallory's anilin blue, Lee-Brown modification of Mallory's anilin blue, Bielschowsky–Maresch, Bielschowsky–Perdrau (Bailey and Hiller), Bielschowsky–Ferguson, Bielschowsky–Foot, Hortega–Foot silver carbonate.

The technique for the three stains which were found to be the most useful is as follows:

(*a*) Mallory's anilin blue (Heidenhain's azan-carmine modification*).

1. 1 per cent azan-carmine G (1 gm. in 100 cc. of water, heat, cool, filter at room temperature and add 1 cc. glacial acetic acid). Thirty to forty minutes in this stain in the paraffin oven at 56° C.
2. Wash in water.
3. Differentiate in anilin alcohol (1 cc. anilin oil in 100 cc. 95 per cent alcohol). Watch under the microscope until the nuclei are red and the cytoplasm pale pink. This step requires from one to three minutes, depending on the thickness of the sections.
4. Remove anilin with acid alcohol, about one minute.
5. Three hours in 5 per cent phosphotungstic acid.
6. Wash quickly in water.
7. Three to six hours in:

anilin blue	0.5 gm.
orange G	2. gm.
glacial acetic acid	8. cc.
distilled water	100. cc.

Boil, cool and filter. Dilute one-half with water.

8. Wash in water.
9. Differentiate in *absolute alcohol, watching under the microscope.*
10. Xylol.
11. Balsam.

* Some changes were made in this technique so the directions do not correspond with the original as given by Heidenhain.

Nuclei orange-red, cytoplasm pink, connective tissue and reticulum blue, fibrin red.

(*b*) Ohmori's rein blau-picric acid.

1. Stain the nuclei with acid fuchsin or lithium carmine at least one-half hour.
2. One minute in rein blau-picric acid (to a concentrated aqueous solution of picric acid add a concentrated aqueous solution of rein blau until a dark green color appears).
3. Differentiate in absolute alcohol.
4. Xylol.
5. Balsam.

(*c*) Mallory's anilin blue, Lee-Brown modification.

1. Phosphomolybdic acid 1 per cent for thirty seconds.
2. Distilled water for 1 to 2 minutes.
3. Mallory's stain:

anilin blue	0.5 gm.	for 1 to 5 minutes
orange G	2. gm.	
phosphomolybdic acid	2. gm.	
distilled water	100. cc.	

4. Distilled water for 2 to 5 minutes.
5. Phosphomolybdic acid 1 per cent for 30 seconds.
6. Distilled water for 1 to 2 minutes.
7. Dehydrate, clear and mount.

The Capsular Basement Membrane: The outer layer of Bowman's capsule is composed of argyrophil fibrils which anastomose with the intertubular stroma of the kidney and with the reticular covering of the tubules. The inner layer of Bowman's capsule is an apparently homogeneous membrane which stains red with Van Gieson, blue with Ohmori and dark blue with the Mallory–Heidenhain azan-carmine. This structure is continuous with the glomerular and tubular basal membranes.

The Capsular Epithelium: These cells form a single layer completely lining the capsule. Their cell borders are distinct and as would be expected from their embryological origin they are directly continuous with the glomerular and tubular epithelium. Their nuclei are elongated, with finely dispersed chromatin and one or more large nucleoli.

Glomerular Epithelium: These are the cells which, in the embryo, form the concave side of the lower limb of the "S" (the convex side of the capsular space). During fetal life and early childhood the arrangement is columnar, this gradually becoming flattened in the adult.

These cells form a complete single layer of covering over the tips and crevices of the capillary tufts. At the hilum they are continuous with the capsular, and thus with the tubular epithelium. They lie outside the glomerular basement membrane which separates them from the endothelium. The arrangement is not syncytial and cell boundaries are easily seen. They are much more numerous than endothelium.

Each cell has abundant cytoplasm and a large oval nucleus situated far from the base. The chromatin is finely dispersed near the nuclear membrane and there are one or two nucleoli. The cytoplasm takes a basophilic tint with Mallory's eosin-methylene blue. The morphology is very similar to that of the capsular epithelium.

Glomerular Basement Membrane: The S-shaped mass of cells destined to form the glomerulus and its tubule is surrounded by a membrane. The portion of this structure covering the concavity of the lower limb of the "S" becomes the glomerular basement membrane. It is closely associated with the glomerular epithelium and is present before the glomerular capillaries appear.

In sections stained with anilin blue or with rein blau the membrane is a single deep blue line lying between endothelium and glomerular epithelium and forms the most striking portion of the glomerular capillary wall. It does not stain with any of the silver impregnation methods used.

For the most part its structure seems to be homogeneous. However, near the hilum there is sometimes a lamellated appearance. Whether the membrane is fibrillar or whether the extra fibrils belong to the connective tissue cells of the vascular pedicle has not yet been determined.

The vas afferens with its supporting framework passes well into the center of the glomerulus before it breaks up into capillaries. Its subendothelial connective tissue seems to fuse with the glomerular basement membrane.

The lumen of each glomerular branch of the afferent vessel is narrowed at fairly regular intervals with openings into numerous small capillary loops. At each of these orifices the basement membrane appears thickened and contracted while in all other portions of the capillary wall it is thin and quite uniform.

The continuity of the glomerular capsular and tubular membranes is evident in any fetal or adult kidney stained with anilin

blue or with rein blau. While differentiating these sections in absolute alcohol the glomerular basement membrane decolorizes before any other membrane or connective tissue in the kidney.

Glomerular Endothelium: These cells are continuous with the endothelium of the vas afferens and efferens and are situated inside the glomerular basement membrane. Their nuclei are widely separated and are much less numerous than those of the epithelium. A continuous layer of cytoplasm lining the membrane and connecting adjacent cells is rarely visible. The nuclei are small and elongated with a thick nuclear membrane and coarse, evenly distributed chromatin. The small amount of cytoplasm at each end of the nucleus makes the cell appear stretched and flattened against the basement membrane. The question of cell boundaries has not been investigated.

There is another type of cell in the wall of the capillary which is probably endothelial also. It is always situated inside the passageway between loops or adjacent to the orifice. In this way it lies next the thickened portions of the glomerular membrane and seems to be almost surrounded by it. This cell cannot be considered epithelial because it is inside the basement membrane. With the stains used in this study the nucleus cannot be distinguished from that of typical endothelium. Its cytoplasm is extremely minute, perhaps because of its position in the constricted portion of the capillary. There is a possibility that it is a connective tissue cell enclosed in the membrane. Further studies on this point are in progress.

Connective Tissue Cells: These accompany the afferent vessel almost to the center of the glomerulus and are always visible in sections through the greatest glomerular diameter. Reticulum argyrophil fibrils also enter at the hilum, pass into the glomerulus and end in finer fibrils or very small clusters. They do not accompany the basement membrane of the capillary loops but seem rather to be associated with the afferent vessel.

Summary

The following conclusions have been reached after studying oil immersion fields of tissues stained as described previously.

1. The glomerular, capsular and tubular basement membranes are continuous and stain red with Van Gieson, blue with Ohmori and

dark blue with Mallory–Heidenhain azan-carmine. The capsule and tubules have an additional external, reticular, argyrophil covering. The glomerular basement membrane is thinner than that of the capsule and tubules. Pores have not been demonstrated, nor any elastic fiber content.

2. The glomerular, capsular and tubular epithelium are continuous. The glomerular epithelial cells have abundant cytoplasm and large vesicular nuclei with one or more prominent nucleoli. These are the only cells which lie outside the glomerular basement membrane. They form complete covering for the loops following closely both tips and crevices. They are arranged in a single layer and not in a syncytium.

3. The glomerular endothelium lies inside the basement membrane and therefore cannot be confused with epithelium. The cytoplasm is very small in amount and the nuclei have a thick nuclear membrane enclosing much coarse chromatin. Endothelial cells are much less numerous than epithelial.

There are cells, probably endothelial, which lie inside the glomerular basement membrane but are partially surrounded by it. Their nuclei seem to be identical with those of typical endothelium and they have very little cytoplasm. Their situation at the orifices between loops makes examination very difficult. Further study to decide their nature is in progress.

4. Connective tissue cells and reticulum fibrils pass in at the hilum accompanying the vas afferens until it subdivides near the center of the glomerulus.

BIBLIOGRAPHY

See following paper for bibliography.

DESCRIPTION OF PLATE

PLATE 104

FIG. 1. Diagram of section through greatest diameter of a normal glomerulus. C. tub. = convoluted tubule; aff. a. = afferent artery; c.t. = connective tissue; c.b.m. = capsular basement membrane; c.ep. = capsular epithelium; gl.ep. = glomerular epithelium; gl.b.m. = glomerular basement membrane; end. = endothelium; end. l. = type of endothelial cell found at passageway between loops; r.b.c. = red blood cell; l. = leucocyte; t. = thickening of glomerular basement membrane often seen at orifice into another loop.

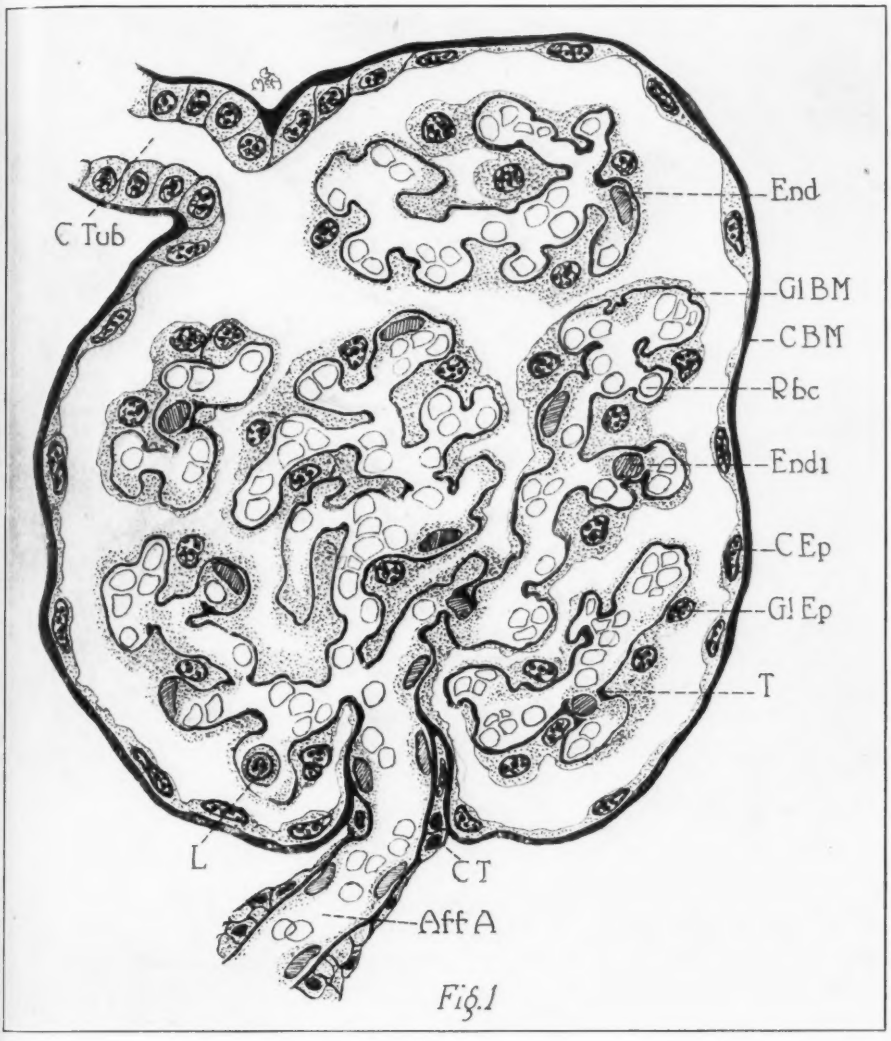

Fig. 1

THE CYTOLOGICAL CHANGES OCCURRING IN THE GLOMERULUS OF CLINICAL GLOMERULONEPHRITIS *

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INTRODUCTION

The object of this paper is to review the literature and to present some new facts regarding the cytological changes occurring in the glomerulus of clinical glomerulonephritis, acute and chronic.

I. REVIEW OF LITERATURE

Richard Bright in 1827 considered the renal lesions in nephritis to be of an inflammatory character. The work of Christison, 1839, Rayer, 1840, Johnson, 1847 and 1850, Frerichs, 1851, Virchow, 1852, and Wilks, 1853, directed attention toward the tubular changes of fatty degeneration, desquamation and proliferation. However in 1850, Johnson observed changes in the glomerular capillary walls in chronic renal disease. From that time on the glomeruli as well as the tubules were studied.

Glomerular Endothelial Reactions: Since most of the very early investigators were convinced of the interstitial and tubular nature of nephritis, very few studies were made of glomerular endothelium. Johnson, 1873, noted that the nuclei in the walls of the glomerular capillaries were abnormally conspicuous. Langhans, 1879, was the first to call attention to endothelial proliferation. Hortoles, 1881, describing a case of scarlet fever, believed the multiplication of the endothelial cells was due to their reversion to an embryonic state. Friedländer, 1883, saw proliferation of "the endothelial tube." Aufrecht, 1886, found a swelling but no increase in number of these cells. In 1885 Langhans' detailed description of the glomerular capillaries in acute nephritis supported what he believed to be the essential lesion, an almost complete occlusion of the loops by endothelial proliferation. Welch, 1886, corroborated this statement. Nauwerck,

* Read before The American Association of Pathologists and Bacteriologists, Chicago, Ill., March 29, 1929.

Received for publication July 20, 1929.

1886, saw endothelial cells with several nuclei and supposed their multiplication was so extensive that they were cast off into the lumen. Ribbert, 1879, and Hansemann, 1887, because of the scarcity of endothelial nuclei in normal glomeruli could not believe they were the source of proliferation in nephritis. Klebs, 1889, differing from his earlier publication, stressed the swelling of endothelium as part of the lesion. Sorenson, 1891, reached the same conclusion. Councilman, 1897, reviewing forty-nine cases of acute and subacute nephritis, confirmed Langhans in the conclusion that most of the nuclear increase was endothelial. Herring, 1900, made a similar observation. Löhlein, 1910, described a proliferation and "net-like arrangement of cellular elements of the endothelial type." Kaufmann, 1911, saw a marked increase in endothelium with desquamation into the capillary lumen. Gaskell, 1911, observed a homogeneous swelling of the capillary wall cells with subsequent fatty degeneration. Aschoff, 1913, Fahr, 1914, Mallory, 1914, MacCallum, 1916, Dietrich, 1917, and Jungman, 1917, all explained the narrowed lumina of the capillary loops as due to endothelial proliferation. Mertz, 1918, in his quantitative study, concluded that between the ninth and twenty-first days of nephritis the endothelial cells at least doubled in number, their increase being proportional to the severity of the disease. Since he believed the number of glomerular epithelial cells to be constant, his figures for endothelial increase are inexact. Herxheimer, 1916, and 1918, in a comprehensive review of war nephritis, stated that the first morphological change was growth of endothelium. Gross, 1919, confirmed Kaufmann as to the proliferation and desquamation of these cells. Mallory, 1914, Ohmori, 1921, Bell and Hartzell, 1922, Munk, 1925, Kuczynski and Dosquet, 1926, Elwyn, 1926, and Hückel, 1928, all described varying degrees of increase in endothelium. MacCallum, 1921, said "the glomerular tufts become greatly enlarged through the appearance of quantities of cells in the lumina of the capillaries, which are not polymorphonuclear leucocytes, but look more like endothelial cells. At least they are mononuclear cells with indistinct outline, so fused together that their origin can hardly be made out." Fahr, 1925, observed such marked proliferation and desquamation that a two to three-celled layer was formed in the capillaries.

Mallory, 1914, Herxheimer, 1916, Gross, 1919, and Elwyn, 1926, have reported mitoses in glomerular endothelial cells.

Intracapillary Leucocytes: The opinion has been uniformly held that a part of the glomerular cell increase was polymorphonuclear. However, Buhl, 1878, and Waller, 1880, decided the leucocyte accumulation was the outstanding feature. Langhans, 1885, stated that leucocytes helped to occlude the glomerular capillaries, their cytoplasm fusing with that of the proliferating endothelium. Cornil, 1879, and Hansemann, 1887, believed the so-called endothelial multiplication was merely an aggregation of leucocytes. Obrzut, 1888, and Ribbert, 1888, both agreed with Buhl and Waller that the leucocytes could later form connective tissue. Gräff, 1916, Herxheimer, 1916 and 1918, and Mertz, 1918, studied in detail the polymorphonuclear exudate. Mertz concluded that in very early stages these cells were increased up to five times their normal number. Aschoff had pointed out that leucocytes in glomeruli might not be due to inflammation, but merely a condition seen in the agonal stage in circulatory disease. After a study of control cases Herxheimer disagreed. Mallory, 1914, called attention to the participation of endothelial leucocytes (large mononuclears or monocytes) in the exudate in slowly progressive cases. He suggested that some wandered in from the blood stream, while others were desquamated endothelium. Bell and Hartzell, 1922, considered the leucocytic reaction polymorphonuclear in type.

Glomerular Intracapillary Network: Cellular and non-cellular types of network within the glomerular loops have been described. In 1849, Rokitansky explained the interference with the glomerular circulation on the basis of a fibrino-albuminous deposit within the capillaries. According to Langhans, 1885, the growing endothelium formed a reticulum within the loops and led to closure of the lumina. To Hansemann, 1887, this conception was erroneous and was apparent only in very thick sections. Klebs, 1889, described obstruction of the capillaries by a syncytium composed of endothelium, leucocytes and masses which stained red with eosin. Thrombotic occlusion of the loops by endothelial cells and leucocytes or by granular masses was seen by Friedländer, 1883, and Nauwerck, 1886. Böhm, 1897, and Kaufmann, 1911, also described an accumulation of fine granular detritus coming from endothelium and blood corpuscles. Fibrin excretion was prominent in the scarlet fever cases studied by Reichel, 1905. Herxheimer, 1916, believed leucocytes were mechanically held in the loops due to injury of the endothelium. He decided coagulated blood serum was the source of the cytoplas-

mic network described by Aufrecht, 1894, as coming from red blood cells. Mallory, 1914, described fibrin in the loops in the form of threads, a network or solid masses. Löhlein, 1910, and Rochs, 1918, observed a coagulated cytoplasmic meshwork within the vessel lumina. Gross, 1919, found free endothelial cells within the network which stained with cresyl violet and Heidenhain's pale blue but not with Van Gieson or Weigert. Ohmori, 1921, saw a deposition of fibrin flakes on the inside of the glomerular basement membrane. These increased in amount, became confluent and crossed the loops. MacCallum, 1916, ascribed the capillary occlusion to the proliferating endothelium and to indefinite foamy masses of cytoplasm. Aschoff, 1921, mentioned the presence of fibrin and nuclei in the cytoplasmic glomerular network. Excessive endothelial cytoplasm alone obstructed the lumen in a case described by Fahr, 1925.

Glomerular Epithelium: Klein, 1877, was the first to mention an increase in nuclei of cells "probably epithelial" covering the tuft. Langhans, 1879, saw such swelling of the cytoplasm and nuclei of these cells that they were attached only by narrow pedicles to the loop wall. When the increase in size progressed far enough they were desquamated in large numbers. Weigert, 1879, and Ziegler, 1879, observed swelling, degeneration and destruction of glomerular epithelium as one of the earliest changes in acute nephritis. Greenfield, 1880, and Saundry, 1880, found proliferation of epithelium, which they called endothelium because they considered it comparable to the peritoneal and pleural lining cells. Litten, 1878, and Dunin, 1883, believed the degenerating epithelium liberated chemicals injurious to the vessel walls and causing inflammation, although Dunin also stated that vascular changes could occur independently of epithelial disease. Aufrecht, 1886 and 1894, described swelling but not proliferation of glomerular epithelium. Kiener and Kelsch, 1882, Cornil and Brault, 1883, Nauwerck, 1886, and Klebs, 1889, all saw multiplication, degeneration, necrosis and desquamation of these cells until the capillary loops were bare. Welch, 1886, and Ribbert, 1888, noted these same epithelial changes. Hansemann, 1887, explained the albuminuria as due to the nakedness of the capillary wall following the desquamation. Ernst, 1893, thought fibrin was able to pass through the glomerular loop after the death of the epithelium. Orth, 1893, and Böhm, 1897, described degeneration of these cells. Herring, 1900, concluded glomerular epithelium was

highly organized and therefore easily injured. Herxheimer, 1909, agreed with Aufrecht, 1886, and with Engel, 1901, that the primary injury in glomerulonephritis is epithelial. Löhlein, 1910, found slight swelling of the epithelium in early stages which passed on to desquamation in severe cases. Kaufmann, 1911, saw both proliferative and degenerative changes. Herxheimer, 1916, observed swelling and the formation of giant cells in this epithelium. Mertz, 1918, on the other hand, decided that the number of epithelial cells was a constant which did not increase. Gross, 1919, felt that endothelial proliferation preceded epithelial degeneration. Mitoses were mentioned in the glomerular epithelium by Mallory, 1914, MacCallum, 1916, Fahr, 1925, Munk, 1925, and Kuczynski and Dosquet, 1926; all showed illustrations of the changes occurring in these cells.

Hyaline granular degeneration of glomerular epithelium similar to that commonly seen in convoluted tubules has been described by Posner, 1880, Aufrecht, 1886, Kaufmann, 1911, Mallory, 1914, Herxheimer, 1916, Gross, 1919, Aschoff, 1921, Fahr, 1925, and Kuczynski and Dosquet, 1926.

Glomerular Connective Tissue Proliferation: Klebs, 1863, stated that in glomerulonephritis the inflammation was situated between the coils of the glomerulus in the small amount of connective tissue there. By 1889, his opinion was modified to the extent that he no longer considered connective tissue proliferation a conspicuous feature. Waller, 1880, confirmed Klebs' original statement because the first nuclear increase occurred between the loops and later progressed toward the tips. Greenfield, 1880, and Böhm, 1897, described a proliferation of connective tissue cells around the vas and between the glomerular loops. Councilman, 1897, and Herring, 1900, thought a few of the new cells were of connective tissue origin. Mallory, 1914, stated that the fibroblasts forming the supporting framework of the capillaries were stimulated to proliferation.

Capsular Epithelial Proliferation: Swelling and proliferation of these cells were first described by Langhans, 1879, Ziegler, 1879, and Greenfield, 1880. The latter two believed the cells to be endothelial with a reaction similar to that of the serous membranes. Saundry, 1880, von Leyden, 1881, Aufrecht, 1886 and 1894, Nauwerck, 1886, Welch, 1886, Ribbert, 1888, Klebs, 1889, Orth, 1893, von Kahlden, 1894, Herring, 1900, Herxheimer, 1909, Löhlein, 1910, Gaskell, 1911, Mallory, 1914, MacCallum, 1916, Aschoff, 1921, Bell and Hartzell,

1922, Fahr, 1925, and Munk, 1925, all confirmed the work of their predecessors on this point.

Hyaline granular degeneration of capsular epithelium has been reported by Aufrecht, 1894, Mallory, 1914, and Fahr, 1925. Mitoses were seen in these cells by Mallory, 1914.

Randerath, 1929, demonstrated anatomically the presence of a pericapsular capillary net. He suggested that bacteria in these capillaries causing an increased permeability of the capsular basement membrane could stimulate the capsular epithelium to proliferation.

Crescent Formation: Langhans, 1879, Nauwerck, 1886, and Fahr, 1925, decided the chief source of the cells in the crescent was desquamated glomerular epithelium. Ziegler, 1879, Greenfield, 1880, Leyden, 1881, Dunin, 1883, and MacCallum, 1916, have ascribed the origin of crescents to capsular epithelium. Saundry, 1880, Welch, 1886, Hansemann, 1887, Orth, 1893, Engel, 1901, Löhlein, 1910, Kaufmann, 1911, Mallory, 1914, Herxheimer, 1916, Aschoff, 1921, and Munk, 1925, have all stated that both capsular and desquamated glomerular epithelium take part in crescent formation. Waller, 1880, and Obrzut, 1888, suggested that emigrated leucocytes changing into connective tissue produced the crescent.

The presence of fibrin in the capsular space and crescent has been reported many times. It was described as a conspicuous feature by Ernst, 1893, Engel, 1901, Löhlein, 1910, Kaufmann, 1911, Mallory, 1914, MacCallum, 1916, Ohmori, 1921, Aschoff, 1921, and Fahr, 1925. Ernst saw a fibrin net between the cells of the crescent and extending into the convoluted tubule. The descriptions of Mallory, Aschoff and MacCallum were very similar. According to Engel, the source of the fibrin was either the blood plasma or the degenerated epithelium. Löhlein explained the fibrin as forming from blood extravasated into the capsular space. Fahr disagreed with this view and described it as an inflammatory excretion. Herxheimer, 1916 and 1918, found no intracapsular fibrin in the war nephritis cases.

Herxheimer described hyaline bodies in the crescent which were not fibrin, which stained yellow with Van Gieson, and which were sometimes inside the cytoplasm of growing epithelial cells. MacCallum also saw hyaline masses in contact with the epithelium and thought they arose from fusion of disintegrating red blood corpuscles which had passed through the capillary wall.

Almost all workers have described coagulated albumin, red blood

cells, polymorphonuclears, desquamated disintegrating glomerular epithelium and fat in the capsular space or in the crescent. Langhans, Gräff and Herxheimer have seen leucocytes passing through the wall of the glomerular loops.

In an explanation of the connective tissue organization of the crescent, Mallory, 1914, stated that fibrin in the capsular space stimulated fibroblasts in the tuft and capsule wherever it touched them. They proliferated and organized until the fibrin was replaced by collagen. MacCallum, 1916, believed the proliferating epithelial cells brought with them a supporting framework of connective tissue.

Changes in Permeability of Glomerular Capillary Wall: The large amount of exudate in the tubules and capsular spaces in nephritis has suggested an increased permeability of the glomerular capillary walls. No one has been able to demonstrate stomata or other morphological evidence of this process. Toynbee, 1846, and Thoma, 1877, showed experimentally that in normal kidneys, injections of a calcium solution and Berlin blue at a pressure of 50 mm. Hg. very rarely went through the loops into the capsular space. On the other hand, in nephritic kidneys, the more severe the disease the more material passed through the capillary walls. Nauwerck, 1886, Hansemann, 1887, and Engel, 1901, believed the increased permeability was due to the degeneration and desquamation of the glomerular epithelium.

Changes in the Glomerular Basement Membrane: Ohmori, 1921, was the only writer to note changes in the basement membrane in nephritis. He believed it could be mechanically compressed and physically or chemically altered. He observed that it was often attached to the intracapillary hyaline masses seen in old chronic glomerulonephritis. Within the loops fibrin was deposited on the membrane and finally fused with it.

Changes in the Vas Afferens: Langhans, 1879, Nauwerck, 1886, Reichel, 1905, Löhlein, 1910, Mallory, 1914, MacCallum, 1916, Herxheimer, 1918, Gross, 1919, Aschoff, 1921, Bell and Hartzell, 1922, and Fahr, 1925, have all concluded that glomerulonephritis is a primary inflammation in the capillaries of the glomeruli. Other workers have believed the primary change to take place in the vas afferens with a secondary inflammation of the glomeruli. Klein, 1877, after finding a multiplication of muscle and connective tissue nuclei in the coat of the afferent vessel, believed the thickening of

its wall tended to shut off the circulation to the glomeruli. Hlava and Thomayer, 1882, were of the opinion that a small round-celled infiltration in the interstitial tissue around the afferent and efferent vessels compressed their lumina. Aufrecht, 1886 and 1894, confirmed the findings of Klein. Herxheimer, 1918, felt that Aufrecht's conclusions were due to the fact that he was not studying the earliest stages of the disease. Volhard and Fahr, 1914, decided that a spasm of the afferent vessel led to ischemia of the glomerulus and secondary inflammatory processes there. Kuczynski and Dosquet, 1926, described a severe edema in the region of the afferent vessel with occlusion of its lumen in early acute nephritis. The edema stimulated resting cells of the adjacent connective tissue until they wandered into the wall of the vas and formed new cells around the hilum. Hückel, 1928, disagreed with Kuczynski and Dosquet after studying a very early acute case, a woman aged 39 years, who died of uremia thirty hours after the onset of symptoms. He was unable to find swelling or edema at the vascular hilum in more than a very few glomeruli. All workers have agreed that there is a great deal of arteriolar disease in the advanced stages of glomerulonephritis.

Hyalinization of the Glomerulus: Klebs, 1863, concluded that the connective tissue cells between the loops as well as emigrated leucocytes changed into a hyaline substance which later became organized. Klein, 1877, believed there was a primary arteriolar lesion which led to a hyaline degeneration and fibrosis of the glomerulus and its capsule. Thoma, 1877, described a connective tissue change of the vascular loops of the glomerulus. The walls thickened and acquired a homogeneous appearance while the capsule formed concentric layers of fibrous cellular connective tissue. In one type of atrophy the loops did not completely disappear while in the other type they were replaced by concentric layers of connective tissue. Ziegler, 1879, described two types of atrophy, one due to the proliferation and pressure of a crescent on the tuft, the other due to obliteration of the vas afferens. Greenfield, 1880, believed proliferation of glomerular connective tissue cells as well as the crescent led to fibrosis of the glomerulus. Waller, 1880, concluded that the hyalinization of the malpighian body was due to a connective tissue transformation of leucocytes which had migrated into the capsular space. The connective tissue cells normally present between the loops proliferated and assisted in the process. Dunin, 1883, found

three types of contracted glomeruli due to Bright's disease. The types differed in size, fusion or non-fusion of glomerulus and capsule, and partial or total loss of the original lobular structure. Friedländer, 1883, believed the walls of the capillary loops thickened until the lumina were occluded. Nauwerck, 1886, described a hyaline thickening (similar to amyloid degeneration) of the loop walls, plus an occlusion of the capillaries by leucocytes, endothelium and granular masses. Böhm, 1897, observed pericapsular and hilum connective tissue proliferation causing atrophy of glomeruli. Goemans, 1899, described a connective tissue proliferation in the glomerulus and in the capsule. Engel, 1901, believed that organization of the fibrin in the exudate was the source of the connective tissue growth of loops and capsule. Tschistowitsch, 1903, saw pericapsular connective tissue growing in through the capsule at various points and also from the hilum. In some cases swelling of the capsular basement membrane and collapse of the capillaries were the sources of the capsular and glomerular hyalin. Löhlein, 1910, described a homogeneous thickening and hyalinization of the loop walls and fusion of the whole with the capsule. Mallory, 1914, found that a proliferation of fibroblasts in the tuft produced more collagen which contracted toward the hilum until the capillaries were obliterated. This left a non-vascular mass of hyaline connective tissue. Krauspe, 1922, considered glomerular hyaline to be different chemically from capsular hyalin, as shown by their reactions to the Van Gieson stain. He concluded that the two hyaline materials were in a different colloid state. Calcification of the hyaline glomerulus has been reported by several authors.

Summary

1. The opinion has been quite uniformly held that there is a marked proliferation of glomerular endothelium in the acute stages of nephritis.

2. The leucocytic exudate has usually been described as polymorphonuclear. The origin of the mononuclear cells within the capillaries is doubtful, whether from the blood stream or from freed endothelium.

3. Protoplasmic, albuminous and fibrinous types of intracapillary network have been reported. There has been no agreement on this point.

4. Proliferation, degeneration and desquamation of glomerular epithelium have been established as one part of the morphological change.

5. There has been no uniform explanation of the origin and organization of the cells of the crescent.

6. Changes in the vas afferens have been considered for the most part as secondary to the inflammation in the glomerulus.

7. Very little attention has been directed toward alterations in the glomerular basement membrane.

8. The process of hyalinization of glomeruli in nephritis has not been described in detail.

II. Results Obtained from a Microscopic Study of Sixty Cases of Clinical Glomerulonephritis

Sections were stained as described in the previous paper. The descriptions below apply to the Mallory–Heidenhain azan-carmine stain unless otherwise specified.

Glomerular Epithelium: These cells covering the outside of the loops are among the first to react in nephritis. There is a cytoplasmic increase up to two or three times the original amount. With the azan-carmine it appears pale purple and denser than the capsular epithelium. With Mallory's eosin-methylene blue stain the periphery of each cell is basophilic, while the center is acidophilic. The nuclei enlarge and often become indented as if preparing for amitosis. Many cells contain two identical nuclei lying side by side. Mitosis has not been observed. The nuclear membrane is very delicate, and except for one to three nucleoli the chromatin is diffusely distributed in very minute particles. The nuclei are always situated in the periphery of the cell as far from the glomerular basement membrane as possible. Only a thin rim of cytoplasm separates the nucleus from the capsular space. Whether by mitotic or amitotic division, these cells are soon increased to two or three times their original number. This swelling and proliferation occur around every loop in every glomerulus and completely fill in the space normally present between lobules. When cut through the hilum and the junction with the convoluted tubule, the glomerulus appears oval in shape. Often one lobule with its enormous epithelial cells projects into and almost occludes the tubule.

The next change in the epithelium seems to be degenerative. Small hyaline granules and vacuoles appear in the cytoplasm of some of the cells. These bodies stain deep blue and are similar to the hyaline granules so commonly observed in the convoluted tubules in amyloid disease. At the same time the attachment of many of the cells to the loop wall becomes so narrow that it resembles a pedicle (see Fig. 3). This keeps the bodies suspended in the capsular space. The cells are so numerous that in spite of the narrow pedicles the loops are not left bare.

The hyaline granular degeneration may increase until the entire cell is filled. The nucleus may or may not disintegrate. In any case a certain number of cells are desquamated. They lie in the capsular space between fibrin clumps or applied to the capsular epithelium or on the inner surface of a crescent. When the pedunculated shape is retained the glomerular origin is evident, and even when the cell rounds off, its cytoplasm is much denser and more darkly staining than that of the capsular epithelium.

Desquamation is not extensive and soon ceases. Hyaline granular and vacuolar degeneration may continue for some time. As the intracapillary lesions progress, the swelling and proliferation of the glomerular epithelium either stay at a standstill or regress. The cases showing the most desquamation are left with very little epithelium. Bare loops have not been observed.

There is a reason for believing that the degeneration follows proliferation. It is the observation that the earliest intracapillary changes are accompanied by proliferation of epithelium, while the more advanced intracapillary changes seem to be accompanied by degeneration and desquamation.

Glomerular Basement Membrane: During the early stages of glomerulonephritis the changes in the glomerular membrane are rather insignificant. In those glomeruli showing extensive hemorrhage into the capsular space there is much wrinkling and indentation of the membrane, probably due to the external pressure. A careful search was made for pores or tears in the membrane through which the red and white blood corpuscles might have escaped. No openings were found even when the extravasation was so recent that it was not hemolyzed.

Glomerular Endothelium: The endothelial cells lie inside the glomerular basement membrane. They react by swelling and prolifera-

tion so that very early in nephritis there is a complete cytoplasmic wall lining the loops. As many as five mitoses have been seen in one section of a glomerulus. Multiplication continues until there are two or three layers of these cells in each loop (see Fig. 2). The nuclei are now very large and usually elongated due to crowding. Many are deeply indented, the chromatin is coarse, and there may be nucleoli. There is a large amount of cytoplasm, but the outline of each cell is irregular and rather frayed as if it had recently been attached. It appears as if many are desquamated into the lumen, where they are held in a meshwork of leucocytes, fibrin, and hyaline fibers (to be described later). At least in favor of desquamation is the fact that these large mononuclear cells seen in the lumen of the loop are identical morphologically with the adjacent endothelium.

Occasionally pyknosis and karyorrhexis are seen in endothelial cells. This condition is difficult to distinguish from the disintegrating polymorphonuclears, which always seem to stick to the capillary wall.

Glomerular Intracapillary Leucocytes: Polymorphonuclears are not as conspicuous in this series of cases as in those of other authors. In the very early acute cases there are from one to two in each loop, that is, they are about one-third to one-half as numerous as the endothelial cells. When pyknotic they are seen adhering to the capillary wall, while when healthy they remain out in the lumen between the mononuclears. A few eosinophils but no lymphocytes have been observed.

The lumina of the glomerular capillaries are occluded for the most part by mononuclear cells. Some of these may be monocytes. With the stains used in this study neither their nuclei nor their cytoplasm could be distinguished from that of the proliferating endothelium. The numerous mitoses, the adjacent position of these cells and their similar morphology, all point to their endothelial origin. They occasionally appear to be free cells, but usually lie in layers or in a mass. Sometimes the lumen is completely stopped up with cells, but usually there is a narrow slit toward one side of the loop where the circulation may continue.

Neither polymorphonuclears nor mononuclears were ever seen passing through the glomerular membrane. There was no evidence of phagocytosis of disintegrating cell fragments.

Intracapillary Fibrin and Débris: Fibrin in clumps, rods or threads

is occasionally seen in a few glomerular loops. It usually lies close to the capillary wall and takes a bright red color with the Mallory–Heidenhain technique. Coagulated albumin, disintegrating red blood cells and pyknotic polymorphonuclears may be found in the lumina of the loops.

Intracapillary Hyaline Fibers: (Figs. 2 and 3.) It is these hitherto undescribed fibers which eventually lead to hyalinization of the glomerulus. It is believed that they are a typical finding in clinical glomerulonephritis. They were found in all but two of our sixty cases.

These hyaline fibers are present in the earliest stages as fine lines lying between the proliferating endothelial cells and leucocytes. Knots are numerous at intersection points. The fibers with their knots stain deep blue (exactly the color of the glomerular basement membrane) with Mallory–Heidenhain, red with Van Gieson, not at all with silver and are practically invisible with Mallory's eosin-methylene blue and with hematoxylin-eosin. They seem to be attached at one end to the glomerular basement membrane. They always lie along the edge of the cytoplasm of the intracapillary cells. The fibers form a network within the capillary which helps to hold in place the leucocytes and endothelial cells. The occurrence of the fibers is diffuse in most of the loops of almost all glomeruli. They are not seen except in association with endothelial proliferation. Therefore, they are inconspicuous in (1) those cases which show only crescent formation with very little intracapillary lesion and (2) in those glomeruli which are compressed by the hemorrhage in the capsular space.

As the disease progresses, these fibers increase in diameter and in number until they form a dense meshwork enclosing the newly formed endothelial cells. In the earlier stages a few pyknotic polymorphonuclears may be included, but as the fiber meshwork thickens only mononuclear cells remain. The polymorphonuclears have disintegrated. The fibers remain attached to the basement membrane in many places. Usually a narrow channel is left along one side of the loop where the circulation continues. By this time the fibers are much thicker in caliber than the basement membrane of the loop they occupy (Figs. 4 and 5).

The origin of the hyaline fibers is not as yet determined. The possibilities would seem to be: (1) that they are branches or offshoots

from the glomerular basement membrane; (2) that they are fibrin threads which become transformed into collagen; (3) that they are products of disintegrated red or white blood cells; and (4) that they are reticulum or collagen fibers formed intercellularly from the constituents of the blood stream under the influence of a secretion from the proliferating endothelium. In this latter case the disintegrating polymorphonuclears might have some influence.

It should be mentioned that these fibers are believed to be real and not artefacts, because they have not been seen in the sections of numerous normal control kidneys.

The points in favor of the first possibility are the facts that the fibers and membrane are usually attached to one another and that their staining reactions are similar. The demonstration of a fibrillar character in the membrane would give support to this theory.

The work of Baitsell, 1915, 1916, 1917, and 1921, would point toward the feasibility of the second theory. He has shown in living cultures and in wound healing the transformation of a fibrin net into fibrous tissue either by mechanical factors alone or by the influence of living cells. Foot, 1921, believed collagen fibers were a product of the transformation of fibrin, but in 1925 concluded that this was erroneous and that the two were independent of each other. He disagreed with White and Smith, 1924, who believed that fibrin in the center of a tubercle was converted to reticulum by the agency of endothelium. Foot, 1925, demonstrated a reticular network in tubercles one week old before the fibrin appeared. He believes fibrin plays no part in the formation of reticulum and that reticulum is converted directly into collagen. However, the fibers in glomerulonephritis stain blue, while the fibrin is red and both are present at the same time. When first formed, the hyaline fibers are fine sharp lines while the fibrin is usually in coarser rods or clumps. If the fibers do come from fibrin, the colloid state of the latter must be considerably altered and with that its staining reaction and morphology.

With regard to the third possibility, it has been shown by Foot, 1927, that reticulum fibrils in hanging-drop tissue cultures of blood can come from the disintegration of erythrocytes and a rearrangement of the reticulum they contain. He does not suggest that this occurs frequently in the body but that other cells might have an intracellular network which would be deposited by lysis. That red blood cells are not the origin of the intracapillary fibers in glomerulo-

nephritis can be shown with silver impregnation. The disintegrating red cells and their fragments in the convoluted tubules take the silver stain, while in the same section the intracapillary fibers do not.

The fourth possible origin of the fibers involves a discussion of the relation between reticulum and collagen. Russakoff, 1908, first described the transformation of reticulum into collagen. Miller, 1924 and 1927, considered reticulum as precollagen, for in tubercles where there was a tendency to heal, the former became converted into the latter. Baitsell and Mason, 1926, and Baitsell, 1927, have also made a study of the origin of fibrous tissue in tuberculous inflammation. They believe there is a transformation of the intercellular exudate into fibrils and fibrous tissue. "This does not preclude the possibility that the movement of the cells through the exudate may not, by means of purely mechanical factors, change the structure of the fibrous material, or that the secretions of various types of cells may so influence the fibers that their chemical composition becomes changed." The very detailed work of Orsós, 1926, shows that reticulum is only changed collagen and transitions in either direction from one to the other can be seen in normal lymph nodes. He states, and his illustrations show that "excluding certain pathological conditions" reticulum or collagen formation is intracellular. This substance is first seen inside the cytoplasm of the cell as blue-staining elements with Mallory's anilin blue. However, the intracapillary fibers in glomerulonephritis with this same stain seem to be intercellular rather than intracellular. Mallory and Parker, 1927, in a study of reticulum and collagen, concluded that all collagen is produced by fibroblasts, that endothelial cells do not produce an intercellular substance and that reticulum is collagen in a separated form. In order to fit into this theory the intracapillary mononuclear cells in nephritis would have to be considered fibroblasts. Certainly there are no connective tissue cells out in the tips of the loops according to any authority. Yet fiber production is just as plentiful there. According to this study there are only endothelial cells inside the basement membrane of a loop. Therefore the fibroblasts would have to come from endothelium. But the new cells are morphologically more like endothelium than like fibroblasts. The nuclear membrane is thick and often indented, and the chromatin is arranged in rather coarse clumps. These cells do seem to assist in the formation of fibers which ultimately are indistinguishable from collagen. Per-

haps endothelium and its derivatives can produce fibers. Maximow, 1928, studied the formation of reticulum and collagen in cultures of connective tissue and also of blood leucocytes. The process is to be thought of as a crystallization or precipitation. The colloidal sol surrounding the fibroblasts is changed into a gel under the influence of a chemical excretion from the cell bodies. Fiber formation is intercellular. The fibers first appear in the form of an argyrophil network, which is identical with reticulum. With increase in amount, they become parallel and arrange themselves in wavy bundles. At this stage they lose their argyrophil properties and stain blue with anilin blue or red with Van Gieson. Often the fibrin threads form a supporting framework for the fibers, but no direct transformation from one to the other was observed. Above all, the fibers develop extracellularly. The intracapillary glomerular fibers are similar to Maximow's in that they form extracellularly and perhaps from the constituents of the blood. Maximow would explain the newly formed endothelial cells as fibroblasts. On the other hand, the hyaline fibers do not stain with silver even in the early stages but seem to be closely allied to collagen from the beginning.

Thus far in this study it would seem that the hyaline intracapillary fibers in nephritis either come from the glomerular basement membrane or arise intercellularly in a manner comparable to those described by Miller, 1924 and 1927, Baitsell and Mason, 1926, Baitsell, 1927, Mallory and Parker, 1927, and Maximow, 1928. If they arise from the constituents of the blood stream, it must take place under the influence of the proliferating endothelium and disintegrating leucocytes. The fact that the fibers do not stain with silver may be due to lack of sufficiently early stages of nephritis to study.

Glomerular Connective Tissue: As the glomerulus increases in size in the early stages of nephritis, it extends farther down on the vas afferens. Thus more connective tissue cells appear to follow the afferent vessel into the glomerulus. In addition to this apparent increase there is a slight proliferation of these cells. Their location prevents confusion with the intracapillary cellular proliferation. In no case was there seen sufficient proliferation of these cells to occlude the lumen of the afferent vessel. There is a marked increase in reticulum fibrils in contracted glomeruli.

The Capsular Basement Membrane: In the early stages it shows no change. Many authors have described a thickening where it turns

to be reflected over the glomerulus. This was not observed in any of the sixty cases. In later stages the reticular framework thickens and forms multiple concentric layers outside the inner apparently homogeneous basement membrane.

Capsular Epithelium: These cells react similarly to glomerular epithelium. In the early periods of the disease they become swollen, show mitoses and multiply rapidly. They often show hyaline granular degeneration. The intracellular fibrin clumps described by some authors seem on the contrary to be extracellular. The epithelium may form a very cellular single layer or multiple layers.

Crescent Formation: In the cases studied crescents were formed chiefly from proliferating capsular epithelium. When there is marked glomerular epithelial desquamation, the freed cells line the inner surface and may form the inner layers of the crescent. They may be distinguished from the capsular epithelium by their greater size, irregular shape, pedicles and dense cytoplasm. The regularly arranged outer portion of the crescent forms from capsular epithelium. Fibrin lies in threads, sheets and clumps between the cells. It appears bright red with the Mallory–Heidenhain stain. Blue hyaline fibers are also found in threads between the cells. These are very similar to the intracapillary fibers previously described. They have both knobs and knots at intersections. They soon form a meshwork in which the epithelium lies. This often occludes the convoluted tubule. Tubule-like cavities may appear in the crescent. The fibrin, polymorphonuclears and disintegrating desquamated glomerular epithelium soon disappear. The hyaline fibers seem to fuse with the capsular basement membrane. When adhesions develop between crescent and glomerulus, the hyaline fibers of the crescent are continuous with the glomerular basement membrane and through it with the intracapillary fibers. The closely related mesenchymal origin of all the cells in a glomerulus makes it theoretically possible for any one cell to produce fibrils. The origin of the fibers in the crescent is not yet determined. In many areas they seem to come from the capsular basement membrane, while in other places they appear to be forming intercellularly without attachment.

Hyalinization of the Glomerulus: The intracapillary hyaline fibers increase in number and caliber until they form the bulk of the intracapillary glomerular masses. The enclosed mononuclear cells are not allowed much space for cytoplasm. Sometimes the whole loop

is filled with the mass of fibers and cells all the way out to its basement membrane. This allows no lumen for the circulation. When all the loops in a glomerulus are as extensively involved, the nuclei are gradually squeezed out of existence; then adjacent loops fuse. At the same time, if crescents are present the hyaline fibers there increase and press on the enclosed cells until they too disappear. The capsular basement membrane, crescent, glomerular basement membrane and loop contents all fuse. There is a general contraction, and more nuclei disappear. Finally only a hyaline fibrous mass with very few nuclei remains. Even in this end stage it is usually possible with the Mallory–Heidenhain stain to differentiate the capsular and crescent fibers from those of glomerular origin.

Summary

From a microscopic study of glomeruli of sixty cases of acute and chronic glomerulonephritis the conclusions are as follows:

1. The intracapillary cellular increase is chiefly endothelial and is explained by the numerous mitoses. The leucocytes are polymorphonuclear and are much less numerous than the endothelial cells. A small amount of fibrin and débris is found in most of the capillaries.

2. The extracapillary changes consist of proliferation, degeneration and desquamation of glomerular and capsular epithelium. These are easily distinguished from intracapillary lesions because the glomerular basement membrane lies between.

3. Crescent formation may be due to capsular epithelial proliferation or to a combination of capsular proliferation and glomerular epithelial desquamation. In a very early period hyaline fibers appear between the cells and are soon continuous with the capsular basement membrane.

4. Hyaline fibers also appear inside the glomerular capillaries. They stain blue with the Mallory–Heidenhain azan-carmine, or with Ohmori's rein blau and not at all with silver. When first formed, they lie between the proliferating endothelial cells and are usually attached to the basement membrane. They appear as fine sharp lines with knobs at intersections. They soon form a definite meshwork enclosing the intracapillary cells. This fibrous meshwork is be-

lieved to be an important and typical finding in glomerulonephritis. It is the initial stage of the hyalinization of the glomerulus. The process takes place in all the glomeruli but not always to the same degree. When the loops are only partially occluded, blood continues to circulate along one side and the glomerulus has some function. When every loop is occluded, the circulation cannot continue. The fibers within the loop increase in number and caliber, many fuse, and the enclosed cells are atrophied by pressure. The glomerular loop arrives at a stage where it consists of a few flattened epithelial cells, a basement membrane and a lumen completely filled with a hyaline fibrous mass enclosing a few nuclei. Adjacent loops fuse, and the fibers contract. The glomerular epithelium atrophies and disappears. At the same time the fibers of the crescent have increased and contracted until they have eliminated most of the cells. The fibrous crescent now fuses with the fibrous glomerulus. The end result is a sphere of fibrous connective tissue containing practically no nuclei.

5. The origin and composition of the intracapillary hyaline fibers are undetermined and require further study. They do not seem to be fibrin or derivatives of it. They are thought to be a crystallization or precipitation of the intercellular exudate under the influence of the proliferating endothelial cells or perhaps a product of the glomerular basement membrane. Later they are indistinguishable from typical collagenous fibers.

6. The above processes are typical of clinical glomerulonephritis. The finding of a glomerular cellular increase (usually monocytes) following pneumonia and other infections is not to be confused with clinical nephritis. The non-clinical cases do not have the characteristic intracapillary fibrous meshwork.

NOTE: I wish to express my appreciation of the suggestions and criticisms given me by Dr. E. T. Bell during the progress of this study.

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DESCRIPTION OF PLATES

PLATE 105

FIG. 1. One loop of a normal glomerulus. Gl. ep. = glomerular epithelium; gl. b. m. = glomerular basement membrane; end. = endothelium; r. b. c. = red blood cell; l. = leucocyte.

FIG. 2. One loop of a glomerulus from a case of acute glomerulonephritis. Note the swollen, glomerular epithelium, the large endothelial cells in several layers and the intracapillary hyaline fibers. C. b. m. = capsular basement membrane; c. ep. = capsular epithelium; gl. ep. = glomerular epithelium; gl. b. m. = glomerular basement membrane; end. = endothelium; end. 2. = proliferating endothelium; hy. f. = hyaline intracapillary fibers.

FIG. 3. One loop of a glomerulus from a later stage of acute glomerulonephritis. Gl. ep. = glomerular epithelium; gl. b. m. = glomerular basement membrane; end. = endothelium; end. 2 = proliferated endothelium; hy. f. = intracapillary hyaline fibers.

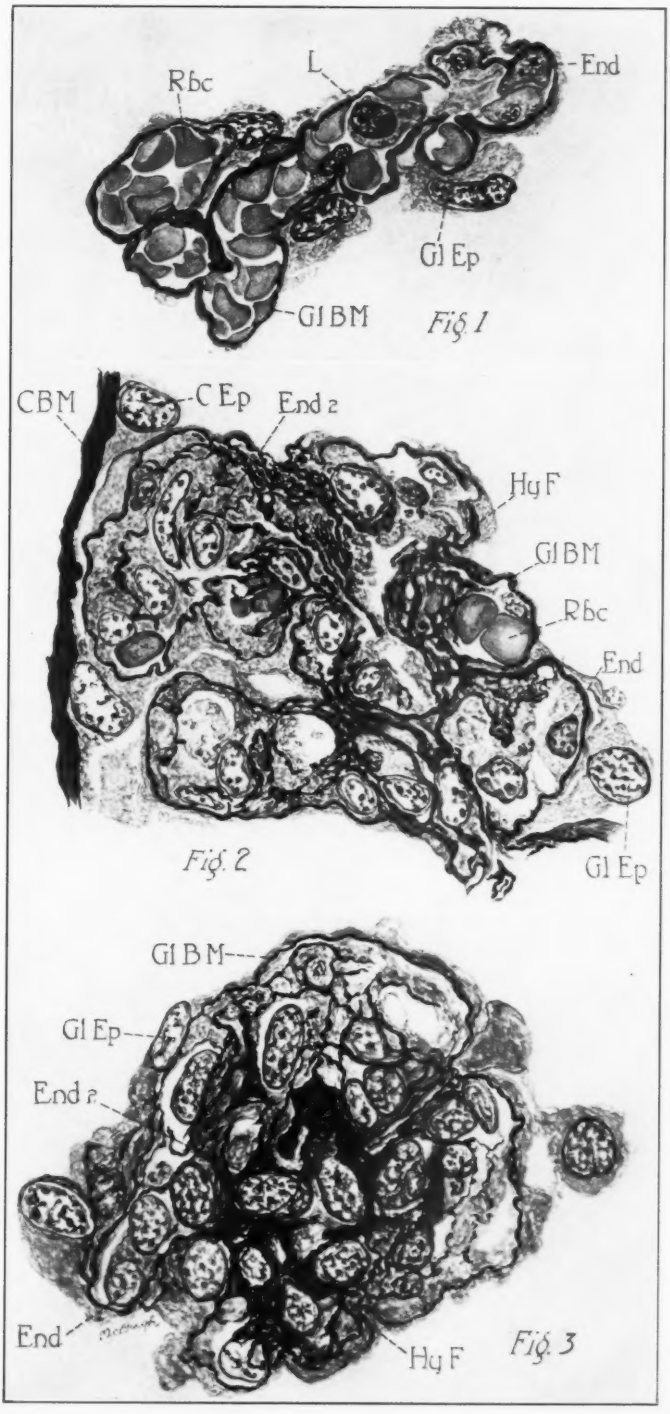
Rbc
L
End
Gl Ep
Gl BM
Fig. 1
CBM
C Ep
End a
Hy F
Gl BM
Rbc
End
Gl Ep
Fig. 2
Gl BM
Gl Ep
End a
End
Hy F
Fig. 3

PLATE 106

FIG. 4. One loop from a glomerulus of chronic glomerulonephritis. Gl. ep. = glomerular epithelium; gl. b. m. = glomerular basement membrane; end. = endothelium; end. 2 = proliferated endothelium; r. b. c. = red blood cell; hy. f. = hyaline fibers.

FIG. 5. One loop from a glomerulus of chronic glomerulonephritis. C. b. m. = capsular basement membrane; gl. ep. = glomerular epithelium; end. = endothelium; end. 2 = proliferated endothelium; hy. f. = intracapillary hyaline fibers.

Figures 1, 2, 3, 4 and 5 are camera lucida drawings from oil immersion fields.

VOICES

X

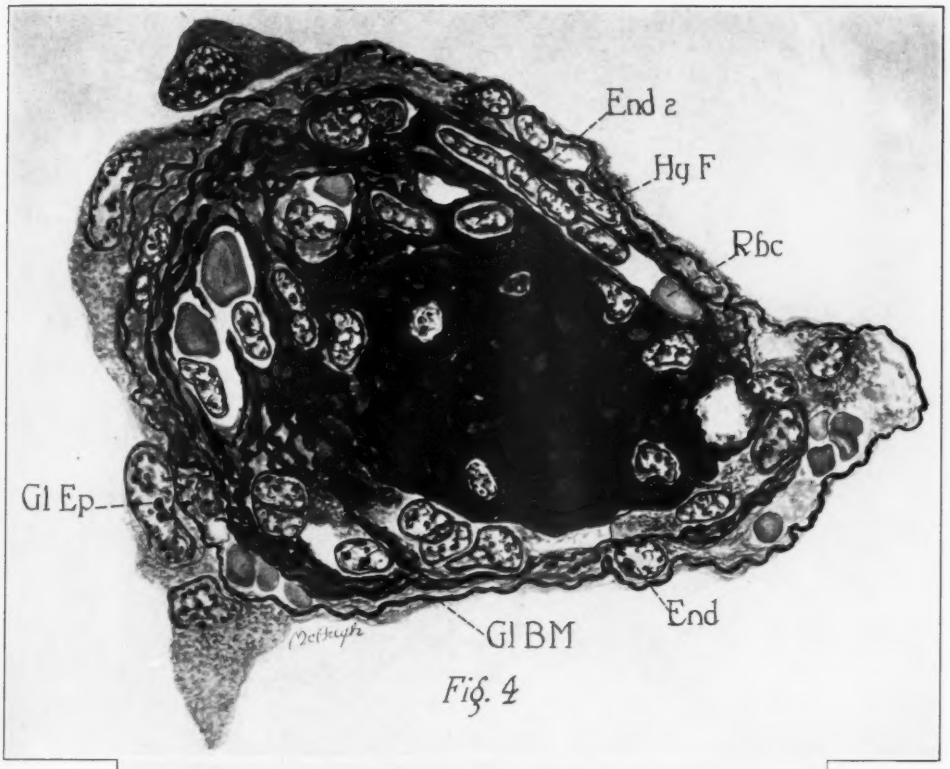

Fig. 4

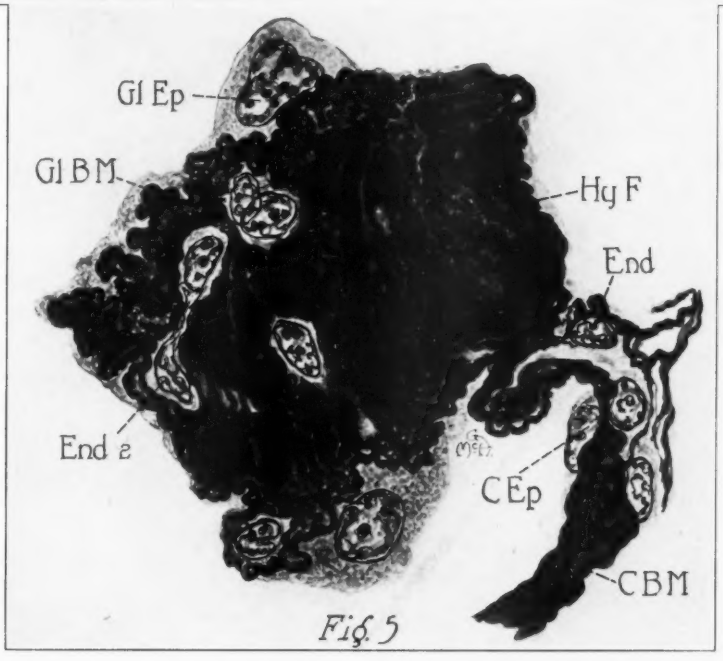

Fig. 5

LIPOID NEPHROSIS *

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Nephrosis is defined as a degenerative renal disease in which the lesions are restricted chiefly to the tubules. On the basis of etiology several types are distinguished:

1. Nephroses due to simple chemical poisons (*e. g.*, corrosive sublimate).
2. Nephroses due to poisons of metabolic origin (*e. g.*, bile acids).
3. Nephroses due to poisons of bacterial origin, as in pneumonia, diphtheria, abscess, etc.
4. Nephroses due to the toxemia of pregnancy.
5. Amyloid nephrosis.
6. Lipoid nephrosis.

This paper deals only with lipoid nephrosis — a type which has attracted much attention in recent years. The study has been directed chiefly toward the structural changes in the kidneys and the anatomical and clinical distinctions between lipoid nephrosis and glomerulonephritis. Some of the questions that have arisen in connection with the problem of lipoid nephrosis are: (1) Is lipoid nephrosis a renal disease or a general metabolic disorder? (2) Is it a distinct type of renal disease or merely a form of glomerulonephritis? (3) What is the nature of the mixed type — nephritis with nephrotic *Einschlag?* (4) Are all the non-contracted kidneys, associated with albuminuria and edema, instances of lipoid nephrosis? (5) Are there any certain clinical or anatomical distinctions between lipoid nephrosis and glomerulonephritis?

The authors chiefly responsible for the wide recognition of lipoid nephrosis as a distinct disease are Munk, Volhard and Fahr, and Epstein. Munk described it under the name of "lipoid nephrosis"; Volhard and Fahr, as "genuine nephrosis"; and Epstein, as "chronic nephrosis." The term suggested by Munk has been generally adopted since it refers to a striking characteristic of the disease.

* Received for publication June 24, 1929.

Lipoid nephrosis was defined anatomically by Volhard and Fahr under the designation of "genuine nephrosis." Nearly all subsequent contributors to this subject have accepted the criteria laid down by these authors. They described the kidneys as enlarged with smooth external surfaces and thickened cortices of yellowish color. The glomeruli appear normal or show only minor focal lesions. Large numbers of lipoid droplets are found in the convoluted tubules, and some may be seen in the interstitial cells and in the glomeruli. There is no tubular atrophy.

Clinically there is general agreement that the outstanding features are the presence of severe albuminuria and marked edema, and the absence of hypertension, cardiac hypertrophy, hematuria and uremia. There is a definite hypercholesterolemia and a decrease of the plasma proteins with reversal of the normal albumin:globulin ratio. Oliguria and decreased elimination of chlorides are frequently noted. The urine commonly contains doubly refractive droplets of lipoid (lipoiduria).

It is not known whether all kidneys with lipoid infiltration of the tubules are associated with the clinical phenomena of lipoid nephrosis. In the present state of our knowledge the diagnosis should not be made on the anatomical findings alone.

Some cases of chronic glomerulonephritis in the earlier stages present the clinical features of lipoid nephrosis, so that a diagnosis based on clinical data alone may be erroneous.

Frequently a renal disease is seen that presents all the clinical features of lipoid nephrosis except for the presence of hypertension or definite nitrogen retention. Epstein included cases of this type in his group of "chronic nephroses"; but they are usually considered a mixed form of nephritis and nephrosis. Fahr refers to this group as nephritis with nephrotic *Einschlag*, which may be translated as nephritis with a nephrotic tendency. The structural changes in the kidneys in this type will be described later.

Table I gives a résumé of all the available published reports in which the diagnosis was established by postmortem examination. The anatomical findings in these cases correspond with Volhard and Fahr's definition.

Table II gives a résumé of the published reports of living persons in which the clinical data seem to justify the diagnosis of lipoid nephrosis. Cases with high blood pressure have not been tabulated

since these are presumably not pure nephroses. When the blood pressure is not recorded the case is excluded because its exact nature is uncertain. Nephroses associated with chronic suppuration have also been omitted since they are presumably of the amyloid type.

In addition to the cases shown in the tables there are reports dealing with groups of patients without individual details. Clausen observed 23 cases of parenchymatous nephritis (nephroses) in children. There were ten deaths. Infection was the chief cause of death. In the single postmortem that was performed the glomeruli showed only a few polymorphonuclear leucocytes.

Schwarz and Kohn observed 17 cases of nephrosis in children. The diagnostic features were albuminuria and edema with hypercholesterolemia and reduced plasma proteins. Blood pressure and renal function are not mentioned. No postmortems were reported.

Bannick and Keith reported 25 chronic nephroses. Their criteria were: edema for several months without demonstrable vascular disease, a blood pressure not above 140/90, blood urea not above 40 mg. per 100 cc., hypercholesterolemia, decreased plasma proteins, no hematuria, no retinitis. There were two deaths but no postmortem reports were given.

Munk, in 1913, reported 5 cases of lipoid nephrosis with albuminuria, edema, lipoiduria and oliguria. Blood pressure was given in only one instance. Four of the patients had syphilis.

Among 300 cases of nephritis with edema, Schlayer found only 6 cases of pure lipoid nephrosis and some of these were uncertain.

Before discussing the several phenomena of lipoid nephrosis in detail, I shall give the results of my own studies on this subject.

Group I. Pure Lipoid Nephrosis

Case I. *Clinical History:* A–28–647. Male, 28 yrs. old. The patient stated that he developed a cold about April 3, 1928, and one week later noticed swelling of the legs and puffiness about the eyes. After a few days the swelling became more prominent and involved the skin of the chest and back. The only subjective symptom was weakness. The urine was dark brown in color and reduced in amount. He was admitted to the hospital April 17, complaining of weakness and edema. Physical findings were negative except for severe generalized edema and moderate tenderness over both kidney regions posteriorly. Hemoglobin was 97 per cent on admission and 81 per cent two weeks later. Erythrocytes were 4,970,000 on admission and 4,600,000 later. Leucocyte count April 17, 7150 with 66 per cent polymorphonuclears. There was a definite oliguria. The specific gravity of the urine was constantly high, 1021 to

TABLE I

Lipoid Nephroses in which the Diagnosis was Confirmed by Postmortem Study

Author	Age in yrs.	Sex	Duration	Outcome	Edema	Urine albumin gm. per 1000 cc.	Cholesterol mg. per 100 cc.	Serum albumin	Serum globulin	Total protein	Blood pressure	Urea nitrogen mg. per 100 cc.	N. P. nitrogen mg. per 100 cc.	Phenolsulphonephthalein	Urine amount in cc.	Wassermann	Basal metabolic rate	Peritonitis	Weight of kidneys in gm.	Lipoiduria
McElroy	17	M	2 mo.	D	3	4					115-75		77		360	−		+		
Kaufmann, Mason	29	M	7 mo.	D	3	5 to 8		Normal ratio			142–98 122–90	24 39		48	2030 0	−		+	570	
Bock, Mayer	43	F	3 mo.	D	3	12					95– 100–85				1700 500			+		
Rigler, Rypins	2½	M	9 wk.	D	3	+++	366	3.08	3.39	6.47	100–80	10.3 20.0								
Murphy, Warfield	21	M	1 yr. +	D	3	++	500 700				118–70 125–65	Normal		60		− −	−10 −15		415	+
Fahr	19	M	6 wk.	D	3	16 to 60					120–		31							+
	38	F	10 mo.	D	+	22 to 60					132–		34		less					
	9	M	2½ mo.	D	3	15 to 25					108–							+		
	18	M	4 wk.	D	3	12 to 30					128–				less					
	7	M	9½ mo.	D	+	+									less					
	16	F	15 mo.	D	+													+		

Volhard, Fahr.....	15	M	15 mo.	D	+	5 to 51					120–58				200 2600			+		
	22	M	6 mo.	D	2	2 to 14					130–90		29 75		550 800			+	510	
Stepp, Petri.....	16	M	6 mo.	D	3	24	960				110– 120–		46		200					
Vandorfy.....	24	M	7 mo.	D	2	3 to 24					135–				800			+	large	
Stolz.....	3	M	1 mo.	D	3	6					80–							+	large	
	51	M	2 yr.	D	1,3	5					120– 105–75							+	large	–
Major, Helwig.....	34	M	10 mo.	D	3	+++		33%	66%		140–90	15		22	less		–31		430	
Löwenthal.....	8	M	2½ yr.	D	3	2 to 28					88–58 120–90	Normal			180 1450					+
	4½	F	17 mo.	D	3	0.5 to 20	400 770		50%	6.5	Normal				100 500					
	29	F	3 mo.	D	3	3 to 28	300				Normal				100 800	–				+
	21	M	4 mo.	D	3	1 to 45	420			3.9	Normal	Normal			300 2600	–			large	+
	16	F	14 mo.	D	3	8 to 12	306				Normal				300 800	–				+

TABLE II

Lipoid Nephroses in which the Diagnosis is Based on Clinical Data

Author	Age in yrs.	Sex	Duration	Outcome	Edema	Urine albumin gm. per 1000 cc.	Cholesterol mg. per 100 cc.	Serum albumin	Serum globulin	Total protein	Blood pressure	Urea nitrogen mg. per 100 cc.	N. P. nitrogen mg. per 100 cc.	Phenolsulphonephthalein	Urine amount in cc.	Wassermann	Basal metabolic rate	Lipoiduria
Campanacci.....	3			Rec.	3	8					Normal							+
	48	F	3 yr.	Rec. alb. +	3	3 to 55					130–		42		600 800	–		+
	18	M		Rec.	2	5 to 6					120– 125–				500 600			±
Epstein, Lande ..	14	F	9 mo.	Imp. alb. +	3	+++	904				125–70	19.6		30			−18	
	27	F	2 yr. (?)	Imp. edema	3	+++	364				110–70	22.4		45		+	−15	
	33	F	7 mo.	Imp. alb. +	2	+++	375				95–60	14		35			−18	
	29	F	5 mo.	Recur	2	+++	508				110–70	18.2		30			−8	
	35	M	12 yr.	Imp. alb. +++	+++ to 0	+++	320			4.3	105–68	15.4					−15	
Rigler, Rypins...	21	F	8 mo.	Imp.	++	+++	330	2.19	5.03	7.2	115–65	9.8 16.0		55		–	−25	
	34	M	13 mo.		+++	+++	Milky	2.7	3.4	6.1	132–84	9.6 33.8		52		–	−12	

Bennett	22	M	18 mo.	Imp. alb. +	++	+++	117 528				140–90 100–70	Norm.				−	−19	
Grossman	27	M	6 mo.	Rec. alb. +	+++	12					120–		44		500 600			+
Murphy, Warfield	25	F	4 yr.	Not rec.	+++ to 0	++	266 388				128–80	16.8		65				+
	24	M	3 mo.	Not rec.	++ to 0		666 275				110–60 130–80	12 20		55 75			+10	
Epstein	28	M	5 mo.	Rec. alb. +	0	+++	300		50%	6.4	130–80		91	15	less			
	32	F	5 mo.	Rec.	+++	+++	840		74.5%	4.38	130–80		54.8	45	less			
Stepp	30	M			0	6 to 8	310				97–	Norm.			2000			
Fanconi	2	M	7 mo.	Rec.	+++	10	338			4.9 5.6	100–		32		less			
Karger, Ullmann	7	F	6½ mo.	Imp. alb. +++	+++ to 0	+++	Milky				95– 110–		31 39					+
Oehlecker	15	M		Rec.	+	8 to 12	370 830				Normal				less			+

1058. A large amount of albumin was constantly present. There were some pus cells and many hyaline and granular casts in the sediment. The Wassermann reaction was negative. The basal metabolic rate was + 27 per cent. Blood cholesterol was found to be 372 mg., 383 mg., and 240 mg. on three separate examinations. Urea nitrogen was 13.5 mg. April 17, 16.7 mg. April 25, and 48.5 mg. May 6. The blood chlorides were 460 mg. April 17, 437 mg. one week later, and 435 mg. May 6. The first intravenous phenolsulphonephthalein test gave 14.6 per cent and the second 27 per cent. The serum proteins were approximately 4 gm., of which the globulin fraction was 97 per cent and the albumin fraction only 3 per cent. Repeated blood pressure determinations gave an average of 120/80. However one systolic reading of 140 mm. Hg. was recorded. A few days before death the patient developed fever with abdominal pain, tenderness and rigidity. A diagnosis of peritonitis was made. Death occurred May 7, twenty-eight days after the onset of the edema.

Postmortem: The necropsy reveals generalized anasarca and a diffuse fibrinopurulent peritonitis. Each pleural cavity contains about one liter of cloudy fluid with abundant fibrin on the surfaces. The heart weighs 315 gm., (body weight, 150 lbs.). There is moderate edema of the lungs. The heart and liver show cloudy swelling. The right kidney weighs 250 gm. and the left 260 gm. The capsules are not adherent. The external surfaces are smooth. The cortices are thicker than normal and pale yellow in color.

Microscopic Examination: Sections stained with hematoxylin and eosin show that there is no tubular atrophy and no disease of arteries or arterioles. Most of the convoluted tubules are dilated. There are no epithelial crescents. The glomeruli are enlarged, but they contain very few erythrocytes. The glomerular capillaries are dilated and under low magnification they appear to be empty, but careful study under high magnification shows that most of them are filled with mononuclear cells that have a very pale vacuolated cytoplasm (Fig. 1). Frozen sections stained with Sudan III show these cells filled with fat droplets. There are also some fat droplets in the epithelial cells of the glomeruli. The cells of the convoluted tubules are filled with fat droplets.

The structure of the glomerulus is seen much better in sections stained by Mallory's anilin blue connective tissue stain (Heidenhain, azan-carmine*) (Fig. 2). The cells that fill the capillaries are clearly seen to be of endothelial origin. They have a large amount of vacuolated cytoplasm, the vacuolization being due to fat droplets

* The reader is referred to McGregor's paper for details of the technique and for the histology of the glomeruli in glomerulonephritis.

that have been dissolved out. The majority of the endothelial cells are firmly attached to the basement membrane, but a few are partially or completely free. The basement membrane of the capillaries shows an uneven thickening. The structure differs from typical acute glomerulonephritis in the absence of hyaline fibers in the capillaries but resembles it in that the capillaries are filled with swollen endothelial cells. The capillaries are distended, but the obstruction is sufficient to interfere with renal function. In sections stained with hematoxylin and eosin the glomeruli were considered practically normal, since the extent of the capillary obstruction was not appreciated.

CASE II. *Clinical History:* A–28–5. Female, age 4 yrs. Admitted to the hospital June 21, 1927. The child had been well until about one week before admission when she developed a cold with a nasal discharge. Edema of the ankles appeared June 19, and no urine was passed during the 24 hrs. preceding admission. There was loss of appetite. The urine showed albumin ++++, and hyaline and granular casts. Leucocytes 11,900. Blood pressure 108/64. Temperature 99° F to 100° F. Profuse drainage from both ears. Maxillary sinuses cloudy on roentgenological examination. Blood urea nitrogen 24 mg. On June 25 both sinuses were drained, and the tonsils and adenoids were removed. Pus was found in the left sinus. Edema became very pronounced. July 5, blood pressure 118/80. No fever. General edema. Ascites. Edema varied from time to time and was not relieved by urea, ammonium chloride or thyroid extract. The blood pressure varied from 108/64 to 118/80. June 22, cholesterol 360 mg., blood urea nitrogen 24 mg., nonprotein nitrogen 50 mg.; June 24, urea nitrogen 20 mg., nonprotein nitrogen 62 mg.; June 30, cholesterol 284 mg., urea nitrogen 18 mg., nonprotein nitrogen 37 mg.; July 11, cholesterol 296 mg.; July 13, urea nitrogen 15 mg., nonprotein nitrogen 49 mg. Discharged Aug. 19, 1927, heavy albuminuria, slight edema.

Readmitted, Aug. 23, 1927, because of recurrence of edema. The edema disappeared on two or three occasions but soon reappeared. Albuminuria varied from + to ++++, and there were many pus cells in the urine. Temperature around 99° F. November 8, urea nitrogen 30.4 mg. November 18, total plasma protein 4.41 gm. Albumin:globulin ratio 1.47. December 10, irrigation of sphenoidal sinus, windows made in maxillary sinuses. Total plasma protein, 3.61 gm. Albumin:globulin ratio 1.11. December 13, hemoglobin 74 per cent, erythrocytes 3,890,000, leucocytes 16,050 — 65 per cent polymorphonuclears. December 30, hemoglobin 53 per cent, erythrocytes 3,130,000. Death Jan. 1, 1928, in convulsions and coma.

Postmortem: Emaciation. No edema. No fluid in serous cavities. Early bronchopneumonia. No peritonitis. Kidneys weigh 95 gm. and 105 gm. The capsules strip easily, and the external surfaces are smooth. The cortices are definitely yellowish in color.

Microscopic Examination: The convoluted tubules are moderately distended, and their cells are filled with fat droplets. There is no tubular atrophy, and the blood vessels are normal. There is very little blood in any of the capillaries. The glomeruli are small and bloodless. There are no epithelial crescents.

The modified Mallory stain (Fig. 3) shows many more endothelial nuclei than are visible in the normal glomerulus. In one area a swollen endothelial cell is seen completely filling a capillary. There is no increase of epithelial cells. Very few leucocytes are found in the capillaries. The basement membrane is uniformly thickened and multilayered, and in several areas it shows a very marked thickening. Some of the capillaries are partially or completely obstructed by swollen endothelium or by the thickened basement membrane. The lesion resembles glomerulonephritis to the extent that there is enlargement and increase in number of endothelial cells.

CASE III. *Clinical History:* A–26–625. Female 6 yrs. old. In December 1925 the patient had a mild cold with some fever and malaise which confined her to bed for a few days. She recovered completely and was well until the middle of January 1926, when her eyelids became puffy and her feet and legs became swollen. This edema persisted. About the middle of March 1926 she was very ill for several days with an infection that was called influenza. The temperature was 102° F. Shortly afterward her abdomen became greatly distended. This distention also persisted. She was admitted to the hospital May 18, 1926. There was severe generalized pitting edema and ascites. The urine showed a heavy cloud of albumin with clumps of pus cells and hyaline and granular casts. May 18, urea nitrogen 27 mg., creatinin 1.5 mg., sugar 0.15 per cent. May 19, phenolsulphonephthalein 10 per cent for 2 hrs. (subcutaneous). June 3, urea nitrogen 19 mg., creatinin 1.4 mg., sugar 0.13 per cent. Phenolsulphonephthalein, 15 per cent for 2 hrs. Hemoglobin 68 per cent, red cells 3,680,000. Leucocytes, 16,800 with 56 per cent polymorphonuclears and 42 per cent lymphocytes. Temperature varied from 99.5° F to 101° F. Pulse 100 to 130. June 22, 1000 cc. of clear fluid removed from the abdomen. The patient gradually grew worse and died on July 3, 1926.

Postmortem: The postmortem reveals a generalized purulent peritonitis, a purulent left hydrothorax and early bronchopneumonia. The heart weighs 60 gm. The kidneys weigh together 275 gm. The external surfaces are smooth, and the cortices are of pale color and somewhat thicker than normal.

Microscopic Examination: Marked distention of many of the convoluted tubules. No material was available for fat or other special stains, but the vacuolated cells indicate strongly that abundant fat

was present. No disease of the blood vessels. No tubular atrophy. The glomeruli are small and bloodless. The capillaries are filled with large endothelial cells as in glomerulonephritis.

CASE IV. *Clinical History:* Male 17 yrs. old. Admitted April 8. The chief complaint was a progressive swelling of the legs of about one months duration, and occasional vomiting. No history of an infection of any kind. The physical findings were negative except for marked edema of the legs and moderate ascites. The urine showed albumin ++++. Blood pressure 120/70. The edema subsided somewhat under hospital care, but on April 24 the patient developed the physical signs and symptoms of generalized peritonitis. The edema increased. April 27, blood urea 106 mg. Blood pressure 120/90. April 30, blood urea 144 mg. Leucocytes 21,400. Death May 6.

Postmortem: Generalized purulent peritonitis. Kidneys 415 gm. and 428 gm. The external surfaces are smooth, and the cortices are very cloudy.

Microscopic Examination: No disease of arteries or arterioles. No hyaline glomeruli. No atrophied tubules. A small amount of fat in the convoluted tubules. Moderate dilatation of the convoluted tubules, and marked distention of the capsular spaces. The glomeruli are not enlarged. The capillary lumina appear to be definitely narrowed or collapsed. The anilin blue stain shows an uneven thickening of the basement membrane which has resulted in narrowing of many capillaries and occlusion of a few. There are only a few endothelial cells in the capillaries, and there are no hyaline fibers.

GROUP II. TRANSITION TYPE — NEPHRITIS WITH NEPHROTIC TENDENCY

CASE V. *Clinical History:* A–28–193. Female 18 yrs. old. Patient was a sex delinquent. Chancre was diagnosed Jan. 1, 1926. Intense antisyphilitic treatment was given (neosalvarsan and mercury) from April to July 1927. Sudden onset of edema July 18, 1927. Antisyphilitic treatment was then discontinued. For the next few days she had oliguria and severe pain over the kidneys. Urine contained albumin +++ at this time. She was kept in bed four months on a liquid diet which contained neither salt nor meat. The edema was generalized and did not decrease appreciably under this treatment. The urinary output was small except when she drank large quantities of water. Albumin decreased to +. In October 1927 she was allowed to get up and was given a general diet. However she soon became troubled with nausea and vomiting, and albumin became +++ again. She had frequent attacks of headache throughout her illness. Wassermann reaction positive June 28, 1926, negative October 1, December 6, 1926, and April 1, 1927. Admitted Nov. 22, 1927, to the hospital. Urine at all times showed a large amount of albumin, doubly refractive lipoids,

many hyaline casts and pus cells and occasional red cells. Hemoglobin 99 per cent. Erythrocytes 5,060,000. Leucocytes 11,400 on admission — differential normal. Phenolsulphonephthalein 70 per cent. Blood urea nitrogen varied from 14.9 to 19 mg. The blood pressure was 160/100 for about three weeks during her stay in the hospital. It was normal on admission and shortly before death. Heart normal. Lungs showed signs of congestion. Septic temperature. Death, Feb. 7, 1928.

Postmortem: Massive anasarca. Acute fibrinopurulent peritonitis. Hydrothorax (1200 cc. right, 700 cc. left). Heart 285 gm. Kidneys together 335 gm., surfaces smooth, cortices yellowish.

Microscopic Examination: No atrophy or dilatation of tubules. Extensive hyaline granular degeneration of many convoluted tubules. Abundant fat in all the convoluted tubules. No disease of arteries or arterioles. The glomeruli are of normal size and contain a relatively small amount of blood so that there appears to be an increase of cells at the expense of the lumina of the capillaries. The anilin blue stain (Fig. 4) shows that most of the nuclei belong to enlarged epithelial cells which compress the capillaries, but there is a definite increase in the number of endothelial nuclei. The basement membrane is definitely thicker than normal. The glomerular lesion consists chiefly in enlargement of the epithelial cells and thickening of the basement membrane with resulting narrowing of the capillaries.

The only clinical distinction from pure lipoid nephrosis is the presence of hypertension.

Case VI. *Clinical History:* A–28–183. Female, 34 yrs. old. Well until June 1, 1927, when she first noticed unusual fatigue and drowsiness. On June 15 she noticed swelling of the ankles, and the next day her legs were swollen also. In the latter part of July she developed an acute respiratory infection and was very ill with general anasarca, vomiting and suppression of urine. She was told at this time that there was albumin and pus in the urine. Hospitalized for two months. Repeated abdominal paracentesis. Admitted to our service Jan. 4, 1928, complaining of fatigue, drowsiness, anasarca, vomiting and headache. Blood pressure 182/130. Distended abdomen (fluid). Albuminuria with casts. Hemoglobin 48 per cent. Erythrocytes 2,690,000. Leucocytes 9,300. Eyegrounds negative at first but a retinal hemorrhage was observed three weeks later. January 5, urea nitrogen 24.2 mg., creatinin 2.2 mg.; January 9, urea nitrogen 26 mg., creatinin 2.6 mg.; January 18, urea nitrogen 31.2 mg., creatinin 3 mg.; January 30, urea nitrogen 47 mg., creatinin 7.2 mg. Blood pressure January 9, 200/140; January 12, 204/140; January 18, 208/140. The edema gradually decreased under diuretics and low fluid intake, but death occurred on Feb. 6, 1928.

Postmortem: Edema of face, none elsewhere. Ascites. Heart 300 gm. Early bronchopneumonia. Acute rheumatic mitral endocarditis. Left kidney absent. Right kidney 300 gm., external surface smooth, cortex pale.

Microscopic Examination: Moderate diffuse tubular atrophy (Fig. 5). No hyaline glomeruli. No disease of arteries or arterioles. Moderate amount of fat in the convoluted tubules. Dilatation of some of the tubules. The glomeruli are not enlarged, but there is evidently an increased number of nuclei. The anilin blue stain (Fig. 6) shows a great many capillaries partly occluded by large endothelial cells and polymorphonuclear leucocytes. The most striking change is a marked, irregular thickening of the basement membrane, which causes narrowing and sometimes complete occlusion of the capillaries. There is no change in the epithelial cells of the glomerulus. The extensive narrowing and occlusion of the glomerular capillaries are responsible for the tubular atrophy. The obstruction in the glomerular circulation is fairly uniform but none of the glomeruli are completely occluded. The result is a moderate diffuse tubular atrophy with no hyaline glomeruli and no completely atrophied tubules. One enlarged glomerulus was found which showed complete occlusion of all the capillaries by endothelial cells and hyaline fibers, such as is found in typical glomerulonephritis.

CASE VII. *Clinical History:* A–17–145. Male 54 yrs. On the night of Aug. 19, 1916, after working in a cold damp place he suddenly developed edema of the feet. He continued to work, but the swelling grew worse. On September 7 he first noticed edema of both lower eyelids. Admission, Sept. 14, 1916. The urine showed albumin ++, hyaline and granular casts. Hemoglobin 75 per cent, erythrocytes 5,800,000, leucocytes 8000. Blood pressure 155/80. Wassermann reaction negative. Phenolsulphonephthalein, September 15, 72 per cent; September 29, 52 per cent. September 15, urea nitrogen 13 mg., creatinin 4 mg., sugar 0.16 per cent. Discharged Nov. 25, 1916. Readmitted May 17, 1917. On the second admission he complained of marked swelling of the feet and back, severe dyspnea, and gastric distress. He stated that he had felt drowsy and tired most of the time since he left the hospital. Urine: albumin ++, granular and hyaline casts. Hemoglobin 75 per cent, erythrocytes 4,000,000, leucocytes 8000. Blood pressure 190/95; 175/95. July 16, blood pressure 125/95. Wassermann reaction negative. Phenolsulphonephthalein May 19, 35 per cent; July 7, 20 per cent. Urea nitrogen, June 11, 23.7 mg., creatinin 3.2 mg., sugar 0.11 per cent. Death July 21, 1917.

Postmortem: Severe general anasarca, marked ascites and hydrothorax. Edema of lungs, purulent bronchitis and atelectasis. Heart

320 gm. Kidneys together weigh 450 gm., smooth external surfaces, thickened yellowish cortices.

Microscopic Examination: There are a few hyaline glomeruli with atrophic tubules. Many of the convoluted tubules are dilated, and all of them contain fat droplets. There is no disease of arteries or arterioles. The glomeruli are of normal size and contain only a few erythrocytes. Many of them show adhesions to the capsule (Fig. 7). The anilin blue stain shows a general narrowing of the capillaries due chiefly to enlargement of the epithelial cells and thickening of the basement membrane. There are some swollen endothelial cells in the capillaries. The structure is about the same as is shown in Fig. 4. At the site of the adhesions a few capillaries contain hyaline fibers and swollen endothelium as in typical glomerulonephritis.

Group III. Non-Contracted Kidneys of Uncertain Type

These probably belong with the lipoid nephroses, but the available clinical data are insufficient for a definite diagnosis.

Case VIII. *Clinical History:* A–27–511. Female, 43 yrs. old. Present illness began 1 yr. ago with pain in the right upper quadrant and vomiting. Since that time she has had repeated attacks of dyspnea and edema of the ankles. No other past history available. Admitted to the hospital May 6, 1927, 12 hrs. before death, in coma. Severe dyspnea. Slight edema of the ankles. No cardiac murmurs. Blood pressure 110/70. Urine: trace of albumin, no sugar, occasional hyaline casts.

Postmortem: Heart weighs 538 gm., left ventricular hypertrophy, no valvular lesions. No fluid in the serous cavities. Marked edema and congestion of lungs. Liver weighs 2730 gm. and shows moderate fatty metamorphosis. The left kidney weighs 304 gm. The capsule strips easily. The external surface is smooth. The cortex is of grayish yellow color. (No note was made on the right kidney.)

Microscopic Examination: No tubular atrophy. No hyaline glomeruli. Small arteries show a marked increase of elastic tissue. No hyalin in the arterioles. Moderate dilatation of all convoluted tubules A small amount of fat in the convoluted tubules. The glomeruli are large and anemic and show a great decrease in the capillary bed (Fig. 8). The anilin blue stain (Fig. 9) shows a marked irregular thickening of the basement membrane which has resulted

in narrowing of all the capillaries and complete closure of a few. There is a notable increase in the number of endothelial nuclei. Epithelial cells are inconspicuous.

The marked left ventricular hypertrophy indicates that hypertension was present for a long time. The low blood pressure found shortly before death does not exclude a previous hypertension. The possibility that this is a primary hypertension must be considered, but none of the known cases of this disease shows such striking glomerular lesions in the absence of arteriolar disease. The glomerular lesions have some resemblance to advanced chronic glomerulonephritis.

CASE IX. *Clinical History:* A–26–827. Female 62 yrs. old. Admitted Sept. 11, 1926, complaining of generalized edema and dyspnea. Fifteen years ago she was confined to bed for one year with generalized edema. No further information about this attack could be obtained. From that time on her health was fair except for occasional attacks of edema of the ankles and some "stomach trouble." About Aug. 1, 1926, the edema became worse, and she noticed swelling of the abdomen, dyspnea, orthopnea and scanty urine. Her tongue was sore, and she noticed numbness of the hands occasionally. On admission her temperature was 97.7° F; pulse 100; respirations 30; blood pressure 134/82. Dyspnea, edema and weakness were pronounced. The skin and mucosae were pale. Soft systolic murmur at the apex. Ascites. Knee jerks absent. Babinski negative. Hemoglobin 40 per cent. Erythrocytes 1,310,000. The smear showed anisocytosis, poikilocytosis, macrocytes, nucleated reds and polychromatophilia. Leucocytes 2500. Neutrophils 59 per cent, lymphocytes 21 per cent, monocytes 20 per cent. Urine: albumin +++, hyaline and granular casts and a few erythrocytes. Blood urea nitrogen 25.2 mg., creatinin 1.36 mg. Death Sept. 12, 1926.

Postmortem: Marked general anasarca; ascites (7000 cc.); bilateral hydrothorax (150 cc. each). Heart 330 gm. Spleen 37 gm. Red bone marrow in the shafts of the femurs. Kidneys together weigh 260 gm., external surfaces smooth, cortices of normal thickness.

Microscopic Examination: Sclerosis of the larger branches of the renal arteries, but no involvement of small arteries or arterioles. No tubular atrophy. Slight dilatation of the convoluted tubules. The cells of the convoluted tubules contain a small amount of fat and a large amount of blood pigment. All the glomeruli have a hyaline appearance (Fig. 10). The lumina of the capillaries are largely obliterated. The anilin blue stain (Fig. 11) shows that the extreme narrowing of the capillaries is due to a massive thickening of the base-

TABLE

Summary of Clinical Data in

	Case number	Sex	Age in yrs.	Duration	Edema	Albuminuria	Cholesterol mg. per 100 cc.	Serum albumin	Serum globulin	Total protein	Blood pressure	Blood urea mg. per 100 cc.	Urea nitrogen mg. per 100 cc.	N.P. nitrogen mg. per 100 cc.	Phenolsulphonephthalein
Pure lipoid nephrosis	I	M	28	4 wk.	+++	++++	372 383 240	0.12	3.88	4	120–80 140–		13.5 16.7 48.5		14.6 27
	II	F	4	5½ mo.	0 to +++	++++	360 284	2.63 1.90	1.78 1.71	4.41 3.61	108–64 118–80		24.0 20.0 18.0 15.0 30.4	50 62 37 49	
	III	F	6	6 mo.	+ to +++	++							27.0 19.0		10 15
	IV	M	17	7 wk.	+++	++++					120–70	106 144			
Mixed type	V	F	18	7 mo.	+ to +++	+ to ++++					160–100		14.9 19.0		70
	VI	F	34	7 mo.	+++ to +	+++					182–130 208–140		24.2 31.2 47.0		
	VII	M	54	1 yr.	+ to +++	++					155–80 175–95 190–95		13.0 23.7		72 52 35 20
Uncertain types	VIII	F	43	1 yr.	+	+					110–70				
	IX	F	62	15 yr. (6 wk.)	0 to +++	+++					134–82		25.2		
	X	F	52	2 yr.	++										

III

Ten Cases Studied at Postmortem

Oliguria	Wassermann	Basal metabolic rate	Peritonitis	Weight of kidneys in gm.	Possible etiological factors	Fat in tubules	Glomerular lesion
+	−	+27	+	510	Common cold	+++	Capillaries partly obstructed by enlarged fatty endothelial cells. (Figs. 1 and 2)
+			−	200	Common cold, nasal discharge, otitis media, sinusitis.	+++	Swollen endothelium, thickened basement membrane. (Fig. 3)
			+	275	Common cold (?)	+++	Swollen endothelium.
			+	843		+	Uneven thickening of basement membrane, slight endothelial swelling.
+	+		+	335	Antisyphilitic treatment.	+++	Thickened basement membrane, enlarged epithelial cells. (Fig. 4)
			−	300		++	Swollen endothelial cells, thickened basement membrane, rarely glomerulonephritis. (Figs. 5 and 6)
	−		−		Exposure to cold and dampness.	++	Thickened basement membrane, enlarged epithelial cells, focal glomerulonephritis. (Fig. 7)
			−	304 (?)		+	Marked thickening of basement membrane, increase of endothelium. (Figs. 8 and 9)
			−	260		+	Extreme thickening of basement membrane, increase of endothelium. (Figs. 10 and 11)
			+	350		++++	Very large fatty and hyaline epithelial cells, glomerulonephritis. (Fig. 12)

ment membrane. The nuclei all seem to belong to endothelial cells. There is a close resemblance to Case VII (Fig. 8), but the thickening of the membrane is more pronounced and the endothelial cells are less conspicuous.

It is not clear whether death was due to anemia or to renal insufficiency.

CASE X. *Clinical History:* A–27–305. Female 52 yrs. old. History of edema of the legs and ankles for the past two years. She first noticed distention of the abdomen on March 15, 1927. At the same time she had cramp-like abdominal pains and vomited throughout the day. On March 16, she continued to have acute abdominal pain but did not vomit. Admitted March 18. Rapid labored respiration. Crackling râles at the bases of the lungs. Abdomen distended and tender but not rigid. Edema of legs and feet. Temperature 101.8° F. Leucocytes 21,000 — 79 per cent polymorphonuclears. Hemoglobin 80 per cent. Erythrocytes 4,260,000. Death March 18.

Postmortem: Diffuse purulent peritonitis. Heart 315 gm. Edema of lungs. Kidneys together weigh about 350 gm., surfaces smooth, cortices yellowish.

Microscopic Examination: Large numbers of fat droplets in the convoluted tubules, glomeruli and interstitial connective tissue cells. The glomerular fat is very prominent and is situated chiefly in the epithelial cells within the glomerulus and on its surface. About 10 per cent of the glomeruli are hyaline, and these are associated with completely atrophied tubules. The other tubules show no atrophy or dilatation. There is no arterial or arteriolar disease. The glomeruli are large and have an unusual appearance (Fig. 12). The lumina of the capillaries are either greatly narrowed or completely occluded. Large hyaline granules are seen which are chiefly situated within the epithelial cells. The anilin blue stain shows very large epithelial cells filled with hyaline masses. The occluded capillaries are filled with endothelial cells and a network of hyaline fibers such as are found in typical glomerulonephritis. The enlargement of the glomeruli and the narrowing of the capillary lumina are due to two processes: (*a*) marked enlargement of the epithelial cells with fatty and hyaline degeneration, and (*b*) enlargement of endothelial cells and formation of hyaline fibers within the lumina of the capillaries. The disease may be interpreted as a modified form of typical glomerulonephritis.

A summary of the clinical and anatomical data in the ten cases just described is given in Table III.

Discussion of the Various Phenomena of Lipoid Nephrosis

1. *Albuminuria* is a constant finding. Edemas without protein in the urine are not nephroses. In the early stages, in the remissions and in the stage of recovery there may be only a trace, but usually the amount of protein is very large. Amounts as high as 6 per cent have been reported. Epstein estimated that as much as 50 gm. of protein may be excreted daily, and since the total protein in the blood is only about 210 gm., he considers the loss of blood protein one of the most important phenomena of the disease.

Epstein believes that the loss of blood protein in the urine is the cause of the edema in that it results in a decrease of the osmotic pressure of the blood, but there are so many instances of low plasma protein without edema, and *vice versa*, that a causal relationship between albuminuria and edema is uncertain.

2. *Oliguria* is usually noted when the disease is at its peak, but normal or increased output occurs when the edema is lessening. A twenty-four hour excretion of 200 to 800 cc. of urine is frequently seen. A period of anuria was observed in only one case (Kaufmann and Mason).

3. *Lipoiduria* is considered by Munk as pathognomonic of lipoid nephrosis. In his first publication he seems to have considered albuminuria, edema and lipoiduria as sufficient to establish the diagnosis. Doubly refractive bodies are readily demonstrated by attaching a polariscope to an ordinary microscope.

Reference to the tables will show that lipoids were found in the urine in 16 of 19 cases in which they were looked for. Lipoiduria is therefore a rather constant finding in lipoid nephrosis. But Genck has shown that not all doubly refractive bodies in the urine are of fatty nature. Spherocrystals of various kinds are doubly refractive. Lipoiduria has been found in glomerulonephritis (Laweynowicz, 2 of 12 acute cases; Genck, 1 of 6 acute cases; Finger and Kollert, 32 of 76 acute or subacute cases, and 5 of 21 chronic cases; Kollert and Finger, 101 of 289 war nephritics [glomerulonephritis]). It has also been found in diabetes, amyloid disease and pyelonephritis. Tietz found lipoiduria in renal diseases of various types. It is obvious therefore that lipoiduria is not peculiar to lipoid nephrosis.

4. *Lipemia:* An increase of the blood lipoids is found constantly in lipoid nephrosis and usually in glomerulonephritis with edema. The milky serum of nephritics was known to Richard Bright. Erben, in 1904, called attention to the high fat and lecithin content of the blood in nephritics. Chauffard, Laroche and Grigaut in 1911 found hypercholesterolemia in cases of renal edema with albuminuria and noted also that there was no increase of cholesterol in nephritics with nitrogen retention. Epstein has published a series of papers dealing with lipoid nephrosis and glomerulonephritis with a nephrotic tendency. He found hypercholesterolemia a characteristic feature.

Values from 300 to 600 mg. per 100 cc. of blood are commonly reported. Rarely much higher values are recorded (1000 mg. Hahn and Wolff; 1350 mg. Epstein and Lande). Often the serum is of milky appearance, but a high lipoid content may be found when the serum does not have this cloudy appearance (Hahn and Wolff).

The increase of blood lipoid is largely represented by cholesterol, but there is also a marked increase of lecithin and fatty acids (Knaur, Daniels).

Strauss and Schubardt found cholesterol values of over 200 mg. in 6 of 17 cases of acute glomerulonephritis, and in 11 of 44 chronic cases.

Lipemia and renal edema are closely associated. Bennett doubts the occurrence of renal edema without hypercholesterolemia. Maxwell in an extensive study of nephritis found hypercholesterolemia in both acute and chronic forms whenever edema was present. He found only one exception to the rule that renal edema never occurs without hypercholesterolemia.

When uremia develops in chronic glomerulonephritis, the cholesterol sinks to a normal level (Chauffard, Stepp, Maxwell).

Amyloid disease of the kidneys usually shows lipemia. The blood lipoids are usually slightly increased during pregnancy, and in eclampsia there is often a definite increase above the normal level of pregnancy (Hinselmann). An increase has also been noted in sublimate poisoning (Wichert and Russjajewa-Oparina).

Lipemia is not restricted to renal disease. A moderate increase of blood lipoids is often found in diabetes, and sometimes a very marked lipemia is observed. In 25 diabetics Bing and Heckscher found normal lipoid values in 11, moderate increases in 13, and a severe lipemia in one. Strauss and Schubardt found lipoid values in diabetics regularly about 250 mg.

There is often some increase of lipoids in obstructive jaundice (Stepp, Strauss and Schubardt).

Increase of the blood lipoids is a characteristic feature of lipoid nephrosis, but this finding alone does not differentiate this disease from glomerulonephritis with edema, from amyloid nephrosis, or even from certain extrarenal diseases.

Edema may occur without lipemia and *vice versa*, but the close association of edema and lipemia in renal disease suggests a common etiology. Little is known of the underlying causes of lipemia. The fats are believed to come from the ingested food since a pronounced lipemia may be produced in rabbits by intensive cholesterol feeding (Thölldte). It has been suggested that the lipemia in renal disease is due to an inability to utilize fat as it presumably is in diabetes, but Hiller, Linder, Lundsgaard and Van Slyke find that nephritics with constant lipemia burn fat as efficiently as normals.

5. *Edema:* The diagnosis of lipoid nephrosis should not be made if edema has not been present at any time. Apparently only two authors have made this diagnosis in the complete absence of edema, *viz.*, Stepp and Epstein. Epstein's case is obviously chronic glomerulonephritis, and the data in Stepp's case are insufficient for accurate diagnosis. However, in typical cases edema may be absent in the early stages and in the remissions, and it may disappear spontaneously or as a result of treatment.

Edema is commonly severe at the peak of the attack and is often the chief cause of the patient's discomfort. Therapeutic procedures should therefore be directed toward the relief of this symptom when it is pronounced. In general the most successful therapy appears to be a diet with restricted salt and fluid content, and the liberal use of mild diuretics. Epstein strongly recommends a high protein diet on the theory that it will replace the blood proteins lost in the urine. He believes that the edema is due to the loss of plasma proteins in the urine which lowers the osmotic pressure of the blood and results in an excessive accumulation of fluid in the tissue spaces. Edema fluids in nephrosis are poor in protein.

6. *Retention of Sodium Chloride:* There is a retention of sodium chloride in nephrotic edema. It is apparently held in the tissues since it is not increased in the blood. There is no satisfactory evidence that the ability of the kidney to excrete water or salts is seriously impaired. It is possible that edema is due to an injury of the

tissue cells throughout the body which causes them to retain water and crystalloids in the tissue spaces.

7. *Decrease of Plasma Proteins:* Richard Bright knew that the plasma proteins were decreased in nephritis. Erben, in 1904, records a decrease of albumin and globulin and an increase of fibrin in "chronic parenchymatous and subchronic nephritis." In 1905 he observed a shift of the albumin:globulin ratio in favor of globulin so that globulin sometimes exceeded albumin.

Epstein has made extensive studies on the plasma proteins and found them characteristically decreased with reversal of the albumin:globulin ratio in pure lipoid nephrosis as well as the mixed type. In the 10 cases listed in Tables I and II, in which the proteins were studied, they were found decreased in 8. The total protein was greatly decreased in the 2 cases of my series that were studied (Table III), but the albumin:globulin ratio was not reversed in one of them.

The protein lost is almost entirely albumin. Epstein gives an example of a nephrosis in which albumin was 0.466 mg., and globulin 3.462 mg. In one of my cases (Table III) the total protein was 4 mg. of which albumin was 3 per cent and globulin 97 per cent. The normal albumin:globulin ratio is 1.4 to 1.8. Linder, Lundsgaard and Van Slyke found reduction of the plasma proteins with a low albumin:globulin ratio in chronic nephrosis and chronic nephritis with edema but not in nephrosclerosis (hypertension kidney). Fahr and Swanson found a definite reduction of the total plasma protein largely due to loss of serum albumin in 7 of 10 cases of acute and subacute glomerulonephritis. In 5 of 9 cases of chronic glomerulonephritis the total protein was below 6 mg. Decrease of plasma protein evidently does not differentiate lipoid nephrosis from glomerulonephritis.

Epstein believes that edema is due to loss of albumin in the urine and consequent decreased osmotic pressure of the plasma. Low plasma protein and edema are both characteristic of lipoid nephrosis, but they are often not present simultaneously. A low protein level may persist long after edema has disappeared, and intense edema may develop before the blood proteins show any change. It seems more probable that both conditions are due to some underlying cause than that edema is caused by the low protein level.

A decrease of plasma proteins with reversal of the albumin:globulin

ratio has been found in lobar pneumonia in the complete absence of edema and with only a trace of protein in the urine (Geill, Kumpf). Evidently a decrease of protein may occur without a loss in the urine. It has not been proved that the regeneration of plasma proteins is hastened by a high protein diet.

8. *Hematuria:* Macroscopic blood is never found in lipoid nephrosis, but some observers have noticed a few erythrocytes in microscopic preparations. Glomerulonephritis commonly does not show hematuria except in the acute stages and during exacerbations.

9. *Chloride Retention:* When edema is prominent there is usually a decreased elimination of chlorides in the urine. Since there is no increase in the blood it is inferred that the chlorides are retained in the tissues. There is a similar chloride retention in glomerulonephritis with marked edema.

10. *Basal Metabolism:* The basal metabolic rate was low in 13 of the 15 cases in which it was studied (Tables I and II), but this is probably of little significance since the authors do not make corrections for the weight of the edema fluids. G. Fahr * has shown that the basal metabolic rate is usually normal if calculations are based upon the normal weight of the individual.

Epstein believes that certain nephroses are related to myxedema and that they respond favorably to thyroid medication.

11. *Renal Function:* On this point a distinction between lipoid nephrosis and chronic glomerulonephritis is usually made. Whenever a definite nitrogen retention is demonstrable it is assumed that the case is not pure nephrosis but a mixed type (nephritis with nephrotic *Einschlag*). But the various authors do not agree as to the nitrogen level that is admissible to the nephrotic group. It is to be remembered that ordinary mild cases of chronic glomerulonephritis often show no nitrogen retention, and it is uncommon to find urea nitrogen much above the normal except in advanced stages of the disease.

Bannick and Keith in using a level of 40 mg. of blood urea to separate nephrosis from nephritis may have included some cases of glomerulonephritis with the nephroses. In three instances (Table I), in which the postmortem report was pure lipoid nephrosis, there was a definite nitrogen retention. In one of my cases (Case I, Table III)

* Personal communication.

which corresponds to pure lipoid nephrosis in every other respect, the last blood urea nitrogen was 48.5 mg.

It is clear that some cases that are anatomically pure lipoid nephrosis have a moderate nitrogen retention and that many mild cases of chronic glomerulonephritis do not. No instance of pure lipoid nephrosis with uremia has been reported. It may be concluded that renal edema with uremia is not pure lipoid nephrosis, and that with moderately increased or normal blood nitrogen it may or may not belong in this group.

Phenolsulphonephthalein: In the cases reported (Tables I and II) the phthalein excretion is moderately diminished in most instances. The lowest observation was 15 per cent. When phthalein is injected intramuscularly, edema interferes with its absorption and tends to give too low a reading. This may have been the cause of the low reading in Case III (Table III), but in Case I (Table III) the phthalein was injected intravenously. The results with phthalein indicate a moderate impairment of renal function. Chronic glomerulonephritis also shows only a moderate decrease of phthalein elimination before the final stage begins.

12. *Blood Pressure:* It is commonly assumed that when the systolic blood pressure is above 140 mm. Hg. in a case which otherwise has the characteristics of lipoid nephrosis, it is a mixed type, *i. e.*, nephritis with nephrotic *Einschlag*. Volhard states that hypertension is the only symptom by which nephritis with nephrotic *Einschlag* may be distinguished clinically from pure nephrosis. Several authors have reported clinical cases with high blood pressure as lipoid nephrosis, but these have been omitted from Table II. Apparently no extensive studies have been made to determine whether there is an anatomical basis for the exclusion of a case from the "pure lipoid nephrosis" group because of hypertension.

One often sees acute and mild chronic glomerulonephritis with a systolic blood pressure below 140 mm. Hg. There is no justification for classifying all of these as lipoid nephrosis.

13. *Causes of Death in Lipoid Nephrosis:* In the postmortem reports (Table I) it will be noted that eleven of the twenty-four patients died of peritonitis. In the cases in which bacteriological studies were made the invading organisms were found to be pneumococci. Volhard states that all his fatal cases died of pneumococcic peritonitis. Three of my four cases of the pure type and

one of three of the mixed type died of peritonitis (Table III). The tendency to develop peritonitis seems to be characteristic of pure lipoid nephrosis and the mixed type. Of fifty-three examples of typical subacute and chronic glomerulonephritis that I have studied, none died of peritonitis.

Over half of the fatal cases reported died of infections other than peritonitis, such as pneumonia and septicemia. None died of uremia.

14. *Frequency of Lipoid Nephrosis:* Volhard states that he has seen about a dozen cases. Epstein observed 15 cases of "chronic nephrosis" among 193 cases of renal disease, but "chronic nephrosis" includes amyloid kidney, pure lipoid nephrosis and nephrosis with nephrotic *Einschlag*. McElroy diagnosed lipoid nephrosis nineteen times in 600 cases of Bright's disease. Schlayer saw only 6 cases in 300 cases of nephritis and was uncertain of some of these. Bannick and Keith report a surprisingly high incidence — 25 cases of "chronic nephrosis" and 25 cases of "chronic nephrosis of mixed type" in about 90 cases of nephritis. The high incidence noted by these authors is evidently due to their having included as "chronic nephrosis" many cases which others would regard as ordinary chronic glomerulonephritis.

I have made postmortem studies on 53 cases of subacute and chronic glomerulonephritis, 3 that may be called glomerulonephritis with nephrotic *Einschlag*, 4 of pure lipoid nephrosis and 3 of uncertain classification.

15. *Duration and Prognosis:* The duration of the 24 fatal cases (Table I) was as follows: 1 mo., 3; 1–3 mo., 5; 3–6 mo., 3; 6 mo.–1 yr., 6; 1–3 yr., 7. Six cases are recorded (Table II) as having recovered completely, but the great majority still had albuminuria at the time of the report. Munk thinks that most cases of lipoid nephrosis end in healing but albuminuria may last for years or decades. He mentioned one patient who had albuminuria for ten years but was entirely well fifteen years after the onset of her illness. Steinitz thinks that the prognosis is good as to life but poor as to recovery from albuminuria. Volhard mentioned 6 fatal cases among more than a dozen that he had seen.

The duration of my 4 cases of pure lipoid nephrosis was four weeks, seven weeks, five and a half months, and six months, respectively. The 3 cases of mixed type lasted seven months, seven months, one

year respectively (Table III). Dr. G. Fahr has furnished me the record of a patient he has had under observation for four years. He was confined to the hospital about one year, with all the typical features of pure lipoid nephrosis. He left the hospital practically recovered and was entirely free of all signs of the disease three years later.

Examples may be found in the older literature of "chronic parenchymatous nephritis" that recovered. Some of these are no doubt instances of what is now called lipoid nephrosis.

16. *Pathological Anatomy:*

(*a*) *Pure Lipoid Nephrosis:* The kidneys are always enlarged and pale. In one of my cases the combined weight of the two kidneys was 843 gm. The external surfaces are smooth. The color of the cortex varies from pale to yellow. There are always some lipoid droplets in the convoluted tubules and they are often in the glomerular epithelium also, but the amount of fat is not always excessive. There may be only a small amount of fat insufficient to give the cortex a yellow color. The convoluted tubules and capsular spaces are usually dilated. An outstanding feature is the absence of tubular atrophy. Often many of the convoluted tubules are filled with coarse hyaline granules, and these granules may also be found in the epithelial cells of the glomerular tuft both on the surface and between the loops.

The glomeruli are described as normal by nearly all the authors who have reported cases of pure lipoid nephrosis. In fact, normal glomeruli are generally considered necessary to establish the diagnosis of the pure type. However, some observers have realized that they are not entirely normal. Stolz finds them almost normal but containing polymorphonuclear leucocytes. Major and Helwig noted that some glomeruli showed swollen endothelial cells and others contained lipoid droplets. Munk finds no changes at first except some increase of leucocytes. He states, however, that later a definite glomerulitis may develop that leads to a contracted kidney. Volhard finds that the glomerular capillaries are not occluded, but the cells may contain hyaline, granular or lipoid droplets. Fahr noted minor lesions in individual glomeruli in some of his cases. He mentions very slight proliferation, hyaline clumps, collapsed capillaries and fusion between the glomerulus and its capsule.

In sections stained with hematoxylin and eosin the glomeruli appear to be normal except for an increased number of leucocytes in

some of the capillaries, but in sections stained by the anilin blue method definite abnormalities can be made out. In Case I the capillaries were filled with swollen endothelial cells heavily laden with lipoid droplets (Fig. 2). This corresponds with clinical glomerulonephritis except for the absence of hyaline fibers in the capillaries. Case II showed some increase of endothelium and a patchy thickening of the basement membrane (Fig. 3). No special stain could be made on Case III. Case IV showed a fairly diffuse thickening of the basement membrane with narrowing of the capillaries and some increase of endothelium.

The lesions are not exactly the same in any two instances, but they all show enlargement and increase in number of the endothelial cells in some degree as well as thickening of the basement membrane.

In clinical glomerulonephritis the characteristic lesion is a plugging of the capillaries with swollen endothelial cells among which are many hyaline fibers (McGregor). There is therefore a fundamental resemblance to glomerulonephritis, but the endothelial swelling is not so pronounced, there are no hyaline fibers and the capillary lumina are only partially obstructed.

(*b*) *Nephritis with Nephrotic "Einschlag,"* (*Nephritis with Nephrotic Tendency — Mixed Type*): Clinically this type is defined as a disease with all the features of pure lipoid nephrosis except for the presence of hypertension or definite renal insufficiency. I have not found any descriptions of the pathological changes in the kidneys. Cases V, VI, and VII belong to this group. They differ from pure lipoid nephrosis clinically only in the presence of hypertension. Macroscopically the kidneys cannot be distinguished from those of pure lipoid nephrosis.

On microscopic examination lipoid droplets are found in the tubules. The glomeruli show transitions to typical glomerulonephritis in that entire glomeruli (1 case) or parts of glomeruli (1 case) may show the characteristic lesion of glomerulonephritis. Increase in the size and number of the endothelial cells was conspicuous in 2 cases, and thickening of the basement membrane was noted in all 3. Enlargement of the glomerular epithelial cells was the most conspicuous change in one case. The mixed type, nephritis with nephrotic *Einschlag*, therefore resembles both pure lipoid nephrosis and typical glomerulonephritis in that endothelial increase is one of its histological features. The histological structure is not fundamentally

different from that of pure lipoid nephrosis, but there is more obstruction in the capillary bed.

On histological grounds one cannot make a sharp distinction between glomerulonephritis and either the mixed or pure type of lipoid nephrosis. There is a fundamental resemblance in that all three types show endothelial swelling and increase. The differences seem to be in degree rather than in kind.

(*c*) *Renal Lesions of Uncertain Type:* I have studied 3 cases in which the clinical data are inadequate to establish a clinical diagnosis. The kidneys are large and fatty, and there is no tubular atrophy. In the older terminology they would be called chronic parenchymatous nephritis. The glomerular lesions are very prominent. In Case VIII (Figs. 8 and 9) the glomeruli are large, and there is an increase of endothelial nuclei and a marked thickening of the basement membrane with narrowing of the capillaries. In Case IX (Figs. 10 and 11) the thickening of the basement membrane is so extreme that the capillaries are almost obliterated. The clinical picture in this case was that of lipoid nephrosis, *viz.*, severe albuminuria, edema, normal blood pressure and no nitrogen retention, associated with pernicious anemia. However, there was no determination of blood lipoids, and the kidneys had only a small amount of fat.

In Case X (Fig. 12) the epithelial cells are greatly enlarged and they show an extreme hyaline and fatty degeneration. The capillaries contain large endothelial cells and hyaline fibers as in clinical glomerulonephritis. This case is closely related histologically to glomerulonephritis. The enormous accumulation of fat in the kidneys, the edema and the peritonitis are almost sufficient to put it in the clinical group of lipoid nephrosis.

These 3 cases raise the question whether all cases with albuminuria, edema, normal blood pressure and large fatty kidneys should be regarded as lipoid nephrosis regardless of the type of glomerular lesion present.

17. *Etiology:* Munk laid great emphasis upon lues as a causative factor but did not think that all cases were due to lues. Lues is considered an important etiological factor by Volhard, Fahr, Felber, and Karger and Ullmann. However, it is shown in Tables I, II and III that among twenty-one patients examined for lues only three were found to be positive. Syphilis cannot therefore be considered of any particular importance in the etiology of lipoid nephrosis.

Several authors hold the view that lipoid nephrosis is a general metabolic disturbance in which the kidney is affected but that it is not a primary renal disease. Kollert believes that an infection or an intoxication causes a prolonged injury of numerous body cells which expresses itself as a metabolic disturbance. The renal injury is a part of the picture. He offers the same explanation for nephritis with nephrotic *Einschlag*. Knaur does not consider lipoid nephrosis a renal disease. He believes that the primary disturbance is hypotension with resulting poor filtration of water. Schlayer attributes the disease to universal capillary injury. Epstein and Löwenthal regard it as a constitutional disease with secondary renal changes, but not restricted to the kidney. The features which suggest a constitutional disease are the general disturbances such as edema, hypercholesterolemia, alterations in the plasma proteins, etc.

Volhard and Fahr seem to consider lipoid nephrosis as essentially a disease of the renal tubules.

Löhlein, in 1918, expressed the opinion that nephrosis and nephritis with nephrotic *Einschlag* begin as glomerulonephritis and may end with uremia and retinitis. Elwyn has observed several cases of lipoid nephrosis which began as acute diffuse glomerulonephritis.

Clausen stresses the importance of sinus infections. Two of my cases and possibly a third began with a common cold, and another followed exposure to cold and dampness (Table III). This is not unlike the history of acute glomerulonephritis and suggests that infection may be the causative factor.

18. *Is Lipoid Nephrosis Primarily a Renal Disease?* The writers who contend that the disease is a general metabolic disorder with a secondary renal disturbance have not properly appreciated the degree of the renal injury. The glomeruli are regarded as normal, and the only renal lesion is considered to be lipoid infiltration of the tubules. The disturbance of lipoid metabolism and the changes in the blood proteins are regarded as strong arguments in favor of a general disorder.

However, the same disturbances in the blood fats and proteins occur in glomerulonephritis, which is certainly a primary disease of the kidneys. Lipoid nephrosis shows heavy albuminuria and minor disturbances of renal function which must be interpreted as indicating renal damage. There are definite and sometimes pronounced structural changes in the glomeruli, and there are transitions to glo-

merulonephritis both clinically and anatomically. Lipoid nephrosis appears to be a renal lesion in which there is partial but not complete obstruction of the glomerular circulation. Uremia does not develop, but in some unknown way there develops an increased susceptibility to infection, especially to peritonitis.

The Relation of Lipoid Nephrosis to Glomerulonephritis

Clinical Relation: It is obvious from the clinical literature that a diagnosis of lipoid nephrosis is made much more frequently by some physicians than by others. The usual requirements for the diagnosis are albuminuria and edema without definite hypertension or nitrogen retention. When this standard is applied to acute renal disease it undoubtedly includes a great many cases of acute glomerulonephritis, and when applied to chronic renal disease it includes some mild cases of chronic glomerulonephritis. When defined in this way lipoid nephrosis is a fairly common ailment. If, however, we require for the clinical diagnosis severe albuminuria, marked edema, normal or low blood pressure, no nitrogen retention, hypercholesterolemia and low plasma proteins, death from peritonitis or other infections, or a prolonged clinical course marked by repeated exacerbations and remissions, lipoid nephrosis becomes a rare disease and the kidneys at postmortem do not show the characteristic lesions of glomerulonephritis.

Even though we accept the restricted definition of lipoid nephrosis, we encounter many transition cases which cannot be distinguished from glomerulonephritis with certainty. The fact that we recognize a mixed type of nephritis and nephrosis (nephritis with nephrotic *Einschlag*) is an admission that the two diseases blend. The mixed type is particularly difficult to define clinically. How high a blood pressure or how much nitrogen retention is admissible to this group? Both hypercholesterolemia and the decrease of plasma proteins are more pronounced in lipoid nephrosis than in glomerulonephritis, but the difference is only in degree. A patient with lipoid nephrosis never develops uremia, but there may be a decreased elimination of phenolsulphonephthalein or a moderate nitrogen retention. The distinction based on renal function is also in degree only. In fact the two diseases blend in every clinical symptom and test. The clinical evi-

dence indicates strongly that lipoid nephrosis is not a distinct disease but a form of glomerulonephritis that does not tend to develop uremia.

Pathological Relation: The assumption that the glomeruli in lipoid nephrosis are practically normal is largely responsible for the view that the disease is entirely different from glomerulonephritis. When special stains are used which bring out the histological details of glomerular structure it is seen that definite lesions are present in every instance (see Table III for summary), but there is no uniform histological change characteristic of lipoid nephrosis.

Typical clinical glomerulonephritis shows uniformly in the acute stages a plugging of the capillaries with swollen endothelial cells, polymorphonuclear leucocytes and interlacing hyaline fibers (McGregor). In advanced stages the hyaline fibers and the basement membrane enlarge and fuse to give rise to a hyaline glomerulus. The histological features are, therefore: enlargement and increase in number of the endothelial cells, polymorphonuclear leucocytes, hyaline fibers and thickening of the basement membrane. In the 10 nephroses studied (Table III) there was a definite increase in the number and size of the endothelial cells in 8. In 8 of 9 cases in which the basement membrane was seen it was definitely thickened. The thickening was marked in four, and extreme in one instance. Hyaline fibers were found in the capillaries in three instances. Two of the cases showed small glomerular lesions indistinguishable from typical clinical glomerulonephritis, and a third case (Case X) corresponds closely with glomerulonephritis.

It may be said, therefore, that there are many points of resemblance in the glomerular structure of lipoid nephrosis and glomerulonephritis. The chief dissimilarity is that the glomerular capillaries are completely obstructed in glomerulonephritis and only partly obstructed in lipoid nephrosis. But a partial obstruction to the glomerular circulation has a very different effect on the subsequent macroscopic changes in the kidneys and the clinical course from that resulting from a complete obstruction. Complete obstruction produces hyaline glomeruli, atrophied tubules, contracted kidneys and finally uremia. Partial obstruction does not produce any of these four conditions, but the tubules become filled with lipoid, and the clinical course is that of lipoid nephrosis. Some years ago Löhlein called attention to the fact that a damaged glomerulus that

still functions is associated with a fatty tubule. Every case of chronic glomerulonephritis shows such glomeruli with fatty tubules (Fig. 13).

Lipoid nephrosis may therefore be regarded as a form of glomerulonephritis in which the glomerular capillaries are damaged but not completely obstructed. Even from this point of view it is still important to recognize typical cases clinically since it is a form of nephritis that does not terminate in uremia. The patient with this form of nephritis either recovers after a prolonged course or dies from an intercurrent infection.

No instance has come under my observation in which a patient with the clinical picture of lipoid nephrosis subsequently developed a contracted kidney.

Summary and Conclusions

1. A survey of recent literature shows a tendency to use "lipoid nephrosis" in a broad way to include all cases of nephritis with edema, albuminuria, normal blood pressure and normal blood nitrogen. This clinical definition includes many cases that are anatomically acute or mild chronic glomerulonephritis.

2. All the clinical phenomena of lipoid nephrosis, *viz.*, albuminuria, edema, normal blood pressure, hypercholesterolemia, decrease of the plasma proteins with reversal of the albumin:globulin ratio and normal blood nitrogen, may occur in a less pronounced form in glomerulonephritis.

3. There are many transition cases between lipoid nephrosis and glomerulonephritis, *viz.*, those that fit the definition of lipoid nephrosis except for the presence of hypertension or moderate nitrogen retention. These are called the mixed type, or nephritis with a nephrotic *Einschlag*. From the clinical standpoint the two diseases cannot be sharply separated.

4. A histological study has been made of 10 cases of large, fatty kidneys, without tubular atrophy, that were clinically nephritis. Four of these are classed as pure lipoid nephrosis, 3 as nephritis with nephrotic *Einschlag* (mixed type) and 3 as of uncertain type because of lack of clinical data.

5. The glomeruli are not normal in any instance, but the lesions are not of uniform type.

6. In pure lipoid nephrosis there is a varying increase in the number and size of the glomerular endothelial cells and an uneven thickening of the basement membrane.

7. In the mixed type (nephritis with nephrotic *Einschlag*) there is a marked thickening of the basement membrane. In one instance the capillaries were compressed by enlarged epithelial cells. In two instances there was a definite increase in the number and size of the glomerular endothelial cells, and a few areas in the glomeruli showed the changes characteristic of typical clinical glomerulonephritis, *i. e.*, capillaries filled with endothelial cells and a network of hyaline fibers.

8. Three large non-contracted kidneys were studied in which the data were insufficient to determine whether they should be classed as lipoid nephrosis. Two of these showed extreme thickening of the basement membrane. The third showed an enormous accumulation of fat in the tubules and glomeruli, large glomerular epithelial cells with hyaline and fatty degeneration, and leucocytes and hyaline fibers within the capillaries as in glomerulonephritis.

9. Lipoid nephrosis is to be regarded as a form of glomerulonephritis in which the glomeruli are damaged but their capillaries are only partially obstructed so that they continue to function and tubular atrophy does not occur.

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DESCRIPTION OF PLATES

PLATE 107

FIG. 1. Case I. A–28–647. Pure lipoid nephrosis. Hematoxylin-eosin stain. Photomicrograph. The capillaries are largely filled with mononuclear cells with a very pale vacuolated cytoplasm.

FIG. 5. Case VI. A–28–183. Mixed type — Nephritis with nephrotic *Einschlag*. Photomicrograph. Partial occlusion of glomerular capillaries by swollen endothelial cells. Diffuse tubular atrophy.

FIG. 7. Case VII. A–17–145. Photomicrograph. Adhesion of glomerulus to its capsule. The solid portion of the tuft at the site of the adhesion has the structure of typical glomerulonephritis.

FIG. 8. Case VIII. A–27–511. Renal lesion of uncertain type. Photomicrograph. Great increase in number of nuclei. Marked narrowing of the capillaries.

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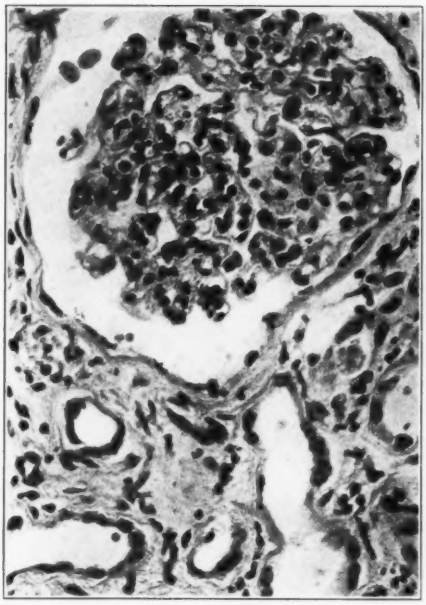

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Bell Lipoid Nephrosis

PLATE 108

FIG. 2. Case I. A–28–647. Pure lipoid nephrosis. Mallory's anilin blue (Heidenhain, azan-carmine). Drawing of lobule of glomerulus (high magnification). The cells filling the capillaries are shown to be of endothelial origin. The vacuoles in the cytoplasm were occupied by lipoid droplets. The majority of the swollen cells (End. a.) are still firmly attached to the basement membrane, but a few are almost completely detached (End. f.) or entirely free. The basement membrane (B. M.) shows a moderate uneven thickening. The capillary lumina (L.) are markedly obstructed. The epithelial cells (Ep.) are inconspicuous.

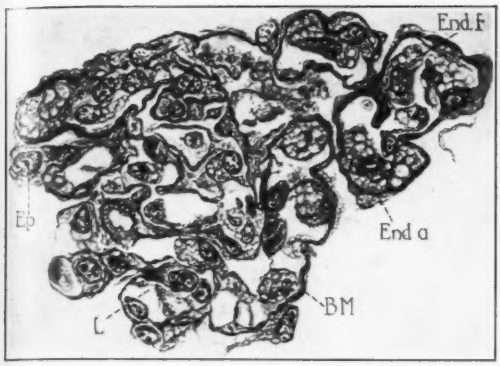
FIG. 3. Case II. A–28–5. Pure lipoid nephrosis. Mallory's anilin blue (Heidenhain azan-carmine). Drawing of part of a glomerulus (high magnification). A number of epithelial cells are seen (Ep.). There are many more endothelial nuclei (End.) than are seen in a normal glomerulus. One large endothelial cell is shown occluding a capillary (End. a.). The basement membrane (B. M.) is moderately thickened throughout, and in several places it shows very marked thickening (B. M. t.). There is partial occlusion of the lumina of some of the capillaries.

FIG. 4. Case V. A–28–193. Mixed type — Nephritis with nephrotic *Einschlag*. Drawing of part of a glomerulus. Stain as in Fig. 3. Prominent glomerular epithelium (Ep.). Increased number of endothelial nuclei. Thick basement membrane (B. M.). Ery., Erythrocytes.

FIG. 6. Case VI. A–28–183. Mixed type — Nephritis with nephrotic *Einschlag*. Drawing of part of a glomerulus. Stain as in Fig. 3. Increased number of endothelial nuclei (End.). Marked thickening of basement membrane (B. M.). Polymorphonuclear leucocyte (P. M. N.). Ery., Erythrocyte; L., lumen of capillary.

FIG. 9. Case VIII. A–27–511. Renal lesion of uncertain type. Drawing of part of a glomerulus. Stain as in Fig. 3. Extreme thickening and duplication of the basement membrane (B. M.). Marked narrowing of lumina of capillaries (L.). Great increase of endothelial nuclei (End.).

FIG. 11. Case IX. A–26–827. Renal lesion of uncertain type. Drawing of part of a glomerulus. Stain as in Fig. 3. The appearances are similar to Fig. 9, but the thickening of the basement membrane is more extreme, the lumina of the capillaries are smaller, and the endothelial nuclei are less conspicuous.



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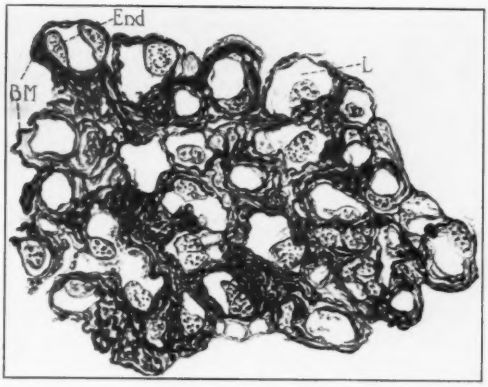

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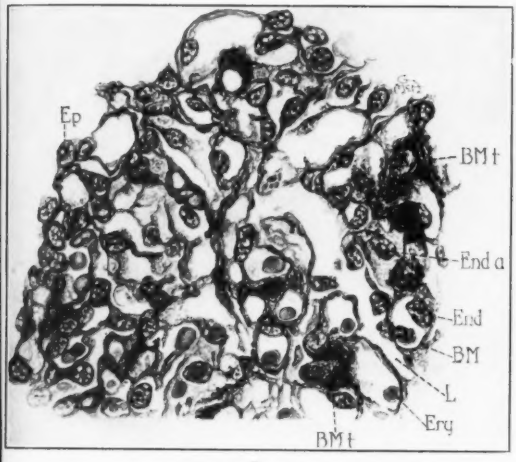

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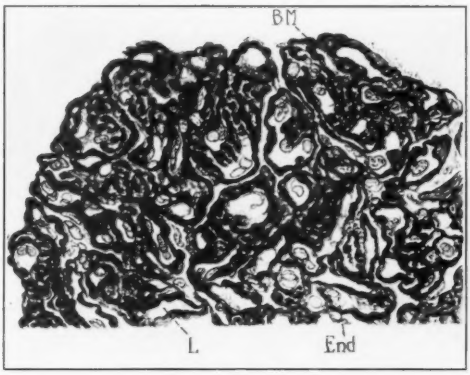

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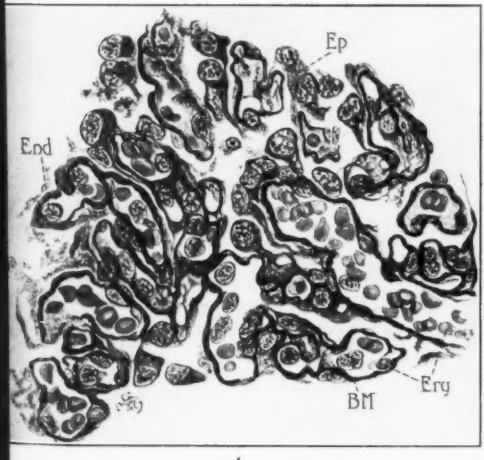

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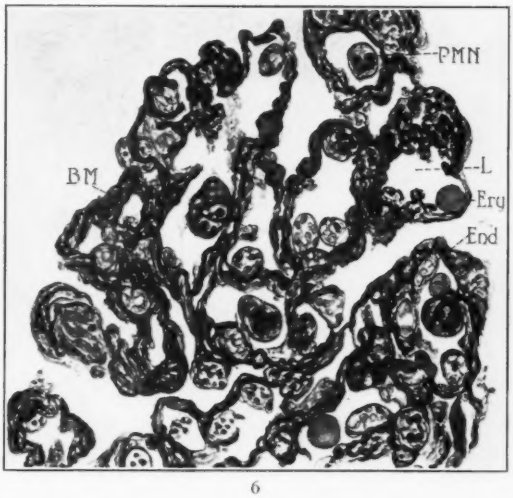


6

Bell

Lipoid Nephrosis

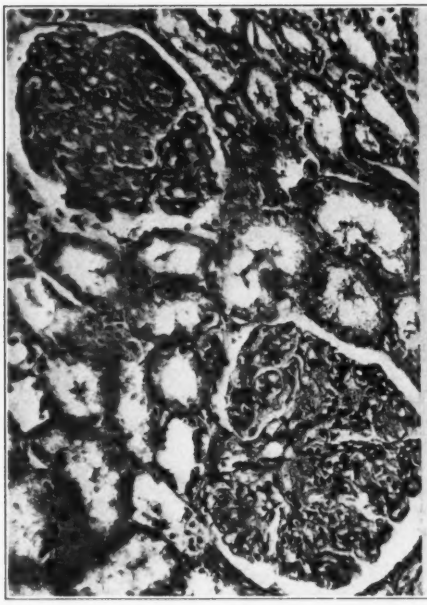
PLATE 109

FIG. 10. Case IX. A–26–827. Renal lesion of uncertain type. Photomicrograph. The glomeruli are of hyaline appearance, but the capillary bed is not completely obstructed. Large convoluted tubules.

FIG. 12. Case X. A–27–305. Renal lesion of uncertain type. Photomicrograph. Enormous enlargement of glomerular epithelial cells. Narrowing and occlusion of capillaries.

FIG. 13. Chronic glomerulonephritis. Photomicrograph. Glomerulus with its associated tubule. The capillaries are markedly narrowed but not completely occluded. The tubule is dilated, and its cells are filled with lipoid droplets.

VOX



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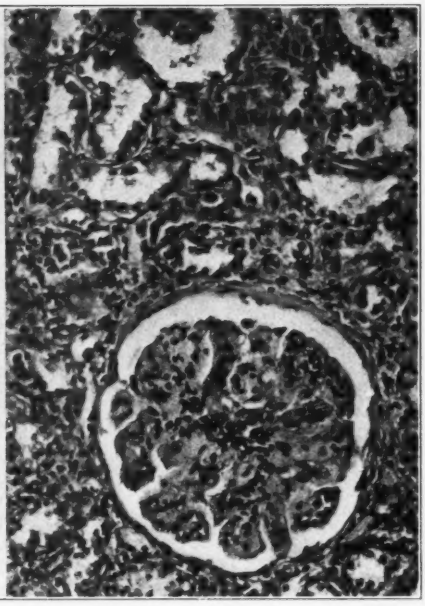

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CARBON TETRACHLORIDE POISONING WITH MACROSCOPIC FAT IN THE PULMONARY ARTERY *

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Since the recent widespread use of carbon tetrachloride in the treatment of hookworm disease in animals and in man, our knowledge of the pharmacological and toxic effect of this drug is rapidly increasing.[1, 2, 3, 4, 5, 6] It is now established that the toxic manifestations are not due to impurities but that they are normal toxicological characteristics of carbon tetrachloride.[7, 8, 9] Clinical and experimental evidence indicate that the toxicity of carbon tetrachloride increases considerably when given with fatty substances or with alcohol, and in man most of the untoward reactions and fatal accidents occurred in chronic alcoholics who had taken alcohol before and after the administration of the drug.[10]

The symptoms of poisoning in man usually appear twelve to thirty-six hours after the ingestion of the drug, and these are characterized by nausea, vomiting, abdominal pain and tenderness. Later jaundice appears.

The most prominent histological changes are found in the liver, but the cortical cells of the adrenal as well as the kidneys are also involved, though to a less marked degree. The blood may be rich in bile pigments, but so far as we know no observations have been reported which show a high fat content of the blood as the result of carbon tetrachloride poisoning.

The case studied is of interest not alone on account of the completeness of the clinical and postmortem observations but also because of the high fat content of the blood and the unusual distribution of this fat in the vascular bed.

Report of Case

Clinical History: F. McG., a laborer, 34 years of age, was admitted in a stuporous condition to the Boston City Hospital, October 29, 1928. His chief complaints were pain in the abdomen and persistent nausea and vomiting.

* Received for publication July 8, 1929.

He has always been exceptionally strong and well, losing work only through periods of intoxication. During the last four years the patient has indulged in alcoholic debauches periodically. The most frequent beverages were "Noonan's Hair Petrol" and denatured alcohol. The patient was admitted to the hospital for one night, one week preceding his present entrance. After leaving the hospital he again drank for three days and on the morning of the third day he drank approximately one ounce of "Carbona" (carbon tetrachloride) in a glass of milk. The same evening he began to feel ill while at a friend's house, but was able to walk home. The following morning a physician was called because the patient suffered continuous abdominal pain, with hiccoughs, nausea and vomiting. The next day these symptoms had temporarily disappeared, but during the evening the pain and nausea recurred, associated with violent attacks of vomiting. The third day after ingesting carbon tetrachloride he became semicomatose and was removed to the hospital.

The family and past history were quite unessential and have little or no bearing on the present illness.

Physical Examination: When examined, he appeared to be well developed and nourished. He was lying quietly, resented any disturbance and was able to answer questions only occasionally. He frequently hiccoughed and vomited foul-smelling, dark fluid material suggesting old blood. His eyes and skin were moderately jaundiced. The skull and hair were normal. The pupils reacted to light but the reaction to accommodation could not be tested. The movements and fundi of the eyes were normal. The nostrils were filled with blood-stained exudate; the breath had a bad odor and the mouth and tongue were coated with a brownish material. The pharynx could not be observed because any attempt at examination induced vomiting.

The thorax was symmetrical and the respiratory expansions were normal. The liver dullness was at the fourth rib in front on the right, and at about the ninth thoracic vertebra behind on both sides. Resonance and breath sounds were normal.

The heart apex was felt in the fourth space in the nipple line. There was no apparent enlargement to percussion and the cardiac sounds were of fair quality and regular. The systolic blood pressure was 150 mm. of mercury and the diastolic 90.

The abdomen was much distended and tympanitic. Shifting dullness in the flanks and a fluid wave in the lower quadrants were both elicited. The liver edge was felt about two inches below the costal margin on the right. The other organs were not palpated since even slight manipulation seemed to induce vomiting. The genital organs were normal, and a rectal examination revealed no abnormal findings, though the patient frequently passed black fluid feces.

The extremities were equal and well developed, and the reflexes were normal.

At the time of admission the temperature was 101° F, which remained essentially unchanged. The heart rate ranged between 100 and 110, and the respirations rose to 30 terminally.

Laboratory Findings: Two specimens of urine showed traces of albumin. The white blood cell count was 13,700 cells per cmm., the red blood cell count 4,600,000 per cmm. with a hemoglobin content of 90 per cent; and the blood platelets were normal. The non-protein nitrogen at the day of death was 115 mg. per 100 cc. of blood. The Kahn test of the blood for syphilis was negative. The stools showed a four-plus guaiac test.

Progress Note: The day after admission the patient became still more uncomfortable and lapsed gradually into almost complete coma. The jaundice became more intense, cyanosis appeared and death followed on October 31, forty-eight hours after admission.

An autopsy was performed six hours postmortem.*

Autopsy Report

The body is that of a large, well developed and well nourished, deeply jaundiced, white, adult male.

Peritoneal Cavity: The surfaces are smooth and bile-stained. The pelvis contains about 15 cc. of reddish brown watery fluid. The diaphragm on the right and left is at the third and fourth intercostal spaces respectively. The lower margin of the liver is 2 cm. below the costal margin in the right midclavicular line and 4 cm. below the tip of the xiphoid process.

Pleural and Pericardial Cavities: Negative.

Heart: Weight 380 gm., is normal in size and contour. A few discrete petechial hemorrhages lie in the epicardium over the right auricle. The endocardium and valve leaflets are discolored greenish brown. Early atheromatous lesions may be followed along the coronary arteries.

Lungs: The lungs are moderately voluminous, heavy, edematous and congested. Scattered punctate hemorrhages are abundant beneath the pleura of both lower lobes. The fresh surfaces are dark red and exude frothy, blood-tinged, watery fluid. The mucosa of trachea and bronchi is deep maroon. The peribronchial lymph nodes are slightly enlarged, soft and unusually red.

Liver: Weight 2600 gm. This organ is uniformly enlarged, rather soft, smooth, greasy and opaque yellow. The fresh surfaces show in addition to the fat, considerable congestion which stands out as a fine red stippling against a yellow background.

Kidneys: Weight 400 gm. They are both enlarged and quite firm. The capsules strip spontaneously from smooth yellowish red surfaces. On section, the cortex is thickened, yellow and opaque and is sharply differentiated from the clearly defined and congested pyramids. The cortex varies from 0.8 to 1 cm. in thickness.

Adrenals: Negative.

* The autopsy was performed by Dr. T. Leary, to whom we are indebted for permission to report his findings.

Aorta: This is thin, smooth, elastic and bile-stained.

Alimentary Tract: There are a few superficial linear erosions along the lower end of the esophagus. A point at the lower end of one of these is surrounded by a small hemorrhage, and on washing away the blood, a tiny bleeding point is visible. The stomach contains about 500 cc. of dark brown fluid.

The Blood: The blood was separately collected and transferred into measuring cylinders from the pulmonary artery, right ventricle, vena cava inferior close to its entrance into the auricle, vena cava inferior close to the iliac veins, and from the pulmonary veins and left ventricle. The bile and blood-stained duodenal contents were also saved for examination.

Within a few minutes the yellow fat in the blood rose to the surface and solidified. It was surprising to observe that as high as 64 per cent of the total blood volume obtained from the pulmonary artery and 25 per cent of that obtained from the upper end of the inferior vena cava was pure fat. Specimens of blood from other sources showed no gross fat. While these figures show only approximate percentages because of the presence of clots in the venous system, they serve to demonstrate the high fat content of the blood in these vessels.

REPORT OF MICROSCOPIC FINDINGS

Sections were fixed in Zenker's fluid, neutral formalin and alcohol-formalin, and embedded in both paraffin and celloidin. Hematoxylin and eosin, and eosin and methylene blue were the routine stains employed, while frozen sections of formalin-fixed material were stained with Sudan IV and Nile blue sulfate.

The most interesting lesions are found in the liver, lungs, brain, kidneys and adrenals. Unfortunately, early postmortem changes have occurred in many of the organs.

Liver: In the eosin-methylene blue preparations little more than a coarse reticulum framework coated by eosin-staining granular debris represents all that is left of the central and mid-zones of the lobules; here, the picture is more suggestive of lung tissue than normal liver. The extreme peripheral portions of the lobules are better preserved, and the cells bordering the portal connective tissue are more nearly normal and show signs of regeneration charac-

terized by an occasional mitosis. Cells of the outer zone, which lie more distant from the portal areas, are greatly distended with large and small clear vacuoles. This zone also shows a slight infiltration with endothelial and polymorphonuclear leucocytes. There are small clumps of alcoholic hyalin in the cytoplasm of a few of the liver cells.

In the frozen sections of the liver stained with Sudan IV, the central and mid-zones of the lobules are filled with large and small irregular confluent globules of fat. Nearer the periphery the fat droplets are more discrete, more uniform in size and are still within the cytoplasm of the liver cells. The hepatic veins are filled with fat, in contrast to the branches of the portal vein and hepatic artery which contain none. With Nile blue sulfate the greater portion of the fat stains pink, whereas only toward the periphery of the lobule does it stain blue, and here it appears as fine and coarse granules.

Trachea and Lungs: The epithelium has largely desquamated from the surfaces of the trachea and larger bronchi. The underlying vessels are congested and the submucous connective tissue is infiltrated with serum, fibrin and red blood cells. Here and there, small groups of alveoli are filled with freshly extravasated blood.

Sections of varying thickness stained with Sudan IV show that while the larger branches of the pulmonary artery contain masses of fat, many of the smaller branches are completely filled; the alveolar capillaries contain but rarely minute fat droplets. There is no visible fat in the alveolar spaces, even in the areas of hemorrhage, nor are there areas of infarction necrosis.

Kidneys: Both the glomerular capsules and tubules contain precipitated albumin, while the tubules in addition contain homogeneous and coarsely granular eosin-staining casts, a few desquamated epithelial cells and an occasional endothelial leucocyte. The tubular epithelium is granular and shows a rare mitotic figure.

When stained for fat, small fat cylinders are visible within the glomerular capillaries, and fatty casts are present in the collecting tubules. The cytoplasm of the cells lining both the convoluted and collecting tubules is filled with small fat droplets.

Brain: Sections of the brain embedded in paraffin and stained with eosin-methylene blue show no pathological lesions. In sections stained with Sudan IV, small fat droplets are quite commonly seen within the capillaries.

Adrenals: Apart from an occasional mitotic figure among the cells of the cortex, there is no other pathological finding.

Esophagus: The epithelium is desquamated and the vessels are everywhere congested. Lymphocytes, endothelial and polymorphonuclear leucocytes and red blood cells infiltrate the submucous connective tissue.

Microscopic Diagnoses: Alcoholic cirrhosis (early); toxic hepatitis; visible fat in vessels of the liver, lung, brain and kidney; tubular nephritis with fatty degeneration of the tubular epithelium; hemorrhages into the submucosa of the trachea and bronchi, and also into the alveolar spaces of the lungs; toxic reaction of the adrenals, and superficial ulceration of the lower end of the esophagus.

DISCUSSION

The most interesting pathological lesions are in the liver, and the study of this organ may largely explain the unusual fatty state of the blood seen at the time of the autopsy. Carbon tetrachloride, in large amounts, is known to exert a distinctly toxic action on the liver, and simulating chloroform in its action it first produces degenerative changes in the cells of the central zones which later extend through the mid-zone into the periphery of the lobule. In small amounts, the liver cells in the central and mid-zones may show simply fatty degeneration, whereas when large quantities are absorbed it causes rapid degeneration and necrosis.

This case is probably best explained on the basis that the patient had a large fatty liver of the type sometimes seen in early alcoholic cirrhosis. The carbon tetrachloride caused degeneration and necrosis of the cells of the central and mid-zones allowing the individual fat droplets to coalesce into larger and irregular masses. This liberated fat gained an easy access to the hepatic system of veins and consequently was carried along into the right side of the heart and out into the pulmonary circulation.

The fact that only a negligible amount of the fat reached the left side of the heart was probably due to the large size of the fat globules, and this also explains why the fat gradually increased in amount in the larger pulmonary arteries.

The small hemorrhages in the epicardium, the connective tissue of the mediastinum, beneath the serosa of the jejunum, and in the

lungs, may be explained either on the basis of an acute cholemia, or an acute toxemia; in the case of the lungs, however, the possibility of fat emboli must also be considered.

In the systemic circulation, fat was seen in the vessels of nearly all the organs as very minute droplets. These minute droplets may have reached these organs as a result of their passage through the pulmonary capillaries, or may have formed in the blood from still smaller droplets, due to the action of carbon tetrachloride on very minute fat globules present in the circulation. Although a few of the capillaries in the brain and in the glomerular tufts of the kidneys revealed even larger droplets which seemed to occlude the lumina, there were no visible embolic lesions.

The superficial ulcerations occurring along the folds of the lower end of the esophagus in cases of chronic alcoholism associated with vomiting have been described recently by Mallory and Weiss.[11] They are considered to be of mechanical and chemical origin and may be the site of fatal hemorrhages.

Summary

1. The gross and microscopic findings are described in an unusual case of carbon tetrachloride poisoning in which the blood in the right side of the heart and larger pulmonary arteries contained an extremely high percentage of fat (60 per cent).

2. The severe damage to the liver, which was already large and filled with fat, was the probable source of the fat in the vascular system.

3. Fat droplets that were small enough to pass through the capillaries of the lung and to gain entrance into the capillaries of other organs produced no microscopic lesions in either the heart, brain or kidney.

4. It appears from these observations that the sensitiveness of alcoholic patients to carbon tetrachloride is increased not only because of increased absorption of the drug, as well as the synergistic action of alcohol and carbon tetrachloride together in producing liver damage, but also because of the possible presence of preëxisting liver damage.

We are indebted to Dr. F. B. Mallory for the photomicrographs, and to Miss Marion Lamb for technical assistance.

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DESCRIPTION OF PLATES

PLATE 110

FIG. 1. Low power drawing of the lung, stained with osmic acid, showing several large, irregular fat globules nearly filling one of the smaller branches of the pulmonary artery. Scattered endothelial leucocytes containing carbon pigment lie in the adjacent stroma.

Fig. 2. Photomicrograph of an area of the liver from a typical case of fatty alcoholic cirrhosis. The fat droplets are regular in distribution and of a fairly uniform size. Sudan IV. × 250

FIG. 3. Photomicrograph of an area from the liver of the case reported. The contrast between this and Fig. 2 is quite marked. The fat is irregular in distribution and is very uneven in the size of globules. Sudan IV. × 250.

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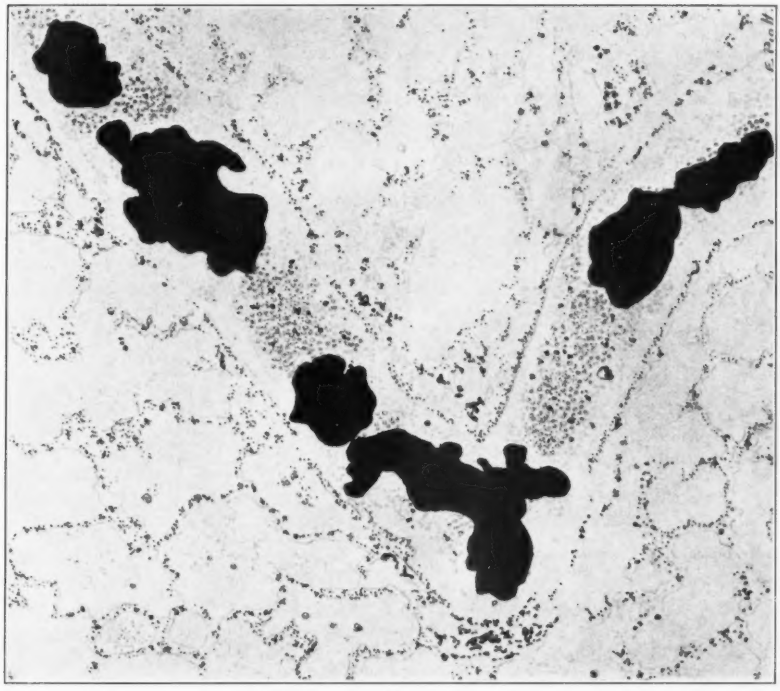

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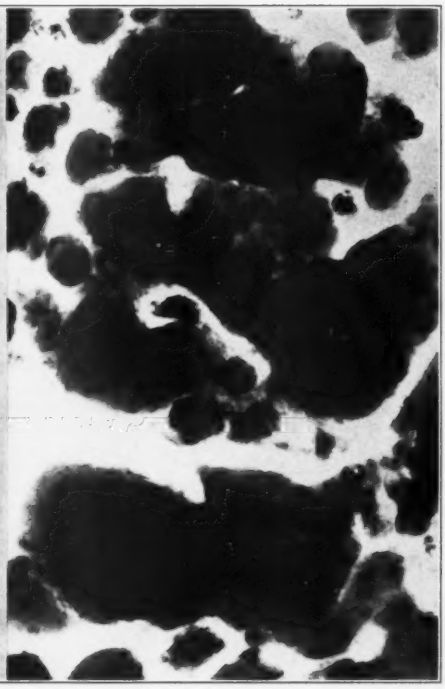

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Plate III

Fig. 4. Blood removed from the pulmonary artery, showing about 60 per cent fat.

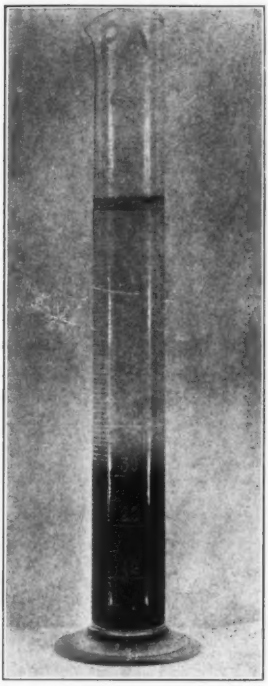
Fig. 5. Blood removed from the pulmonary vein, showing no visible fat.

Fig. 6. Blood removed from the upper portion of the inferior vena cava showing about 25 per cent fat.

Fig. 7. Blood removed from the lower portion of the inferior vena cava. The amount of gross fat is negligible.

Fig. 8. Specimen of bile removed from the gall bladder, showing no visible fat.

Fig. 9. Blood-stained contents of the duodenum and jejunum, showing a narrow rim of fat along the surface.



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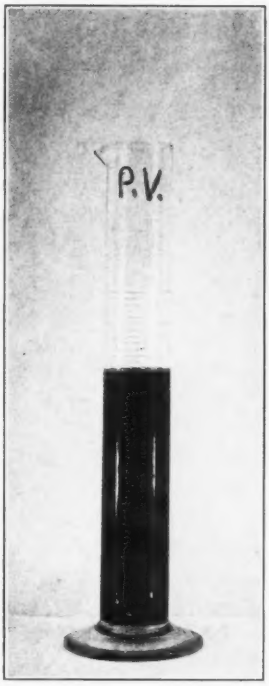

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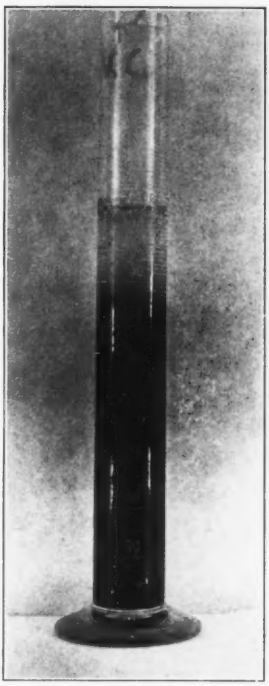

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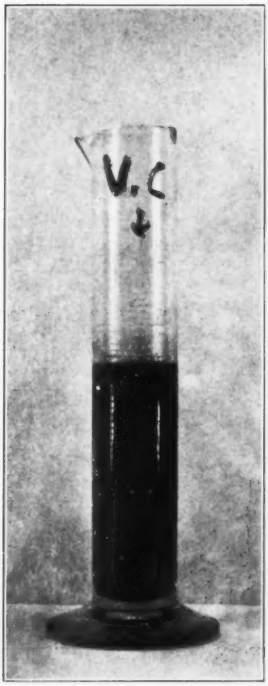

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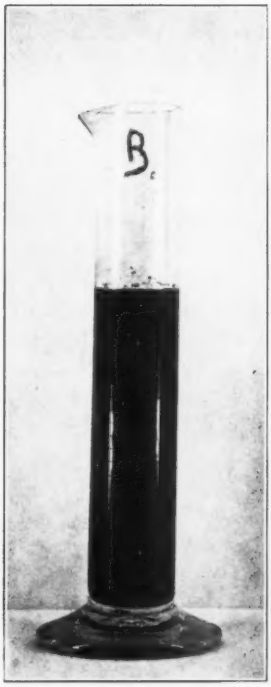

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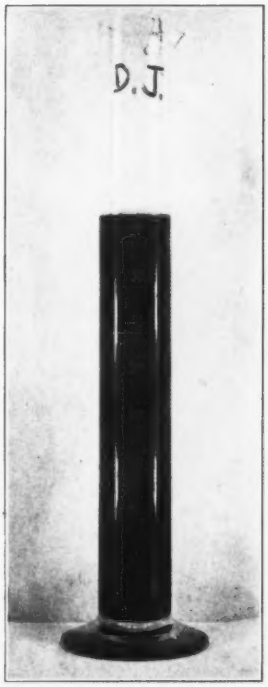

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EXPERIMENTAL OBSTRUCTIVE CIRRHOSIS *

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The term "obstructive cirrhosis" has been chosen to indicate that type of cirrhosis which occurs in a liver simply as the result of prolonged obstruction to the outflow of bile. The term "biliary cirrhosis" has been avoided because it has come to be used in a rather loose manner to indicate any form of cirrhosis which is confined largely to the portal areas, irrespective of the cause.

Already a great deal of work has been done in this field of pathology, much of which was carried out years before aseptic precautions were observed in experimental surgery. And yet, in spite of the rather crude surgical technique of earlier workers, and in spite of infections, hemorrhages and biliary fistulae, the results obtained sixty years ago were not essentially different from those which have been reported in recent years.

Literature

In the year 1866, Leyden [1] and Wyss [2] working independently, reported their findings in dogs following obstruction of the common duct. Many of their animals became infected and died early; a few, however, that lived longer showed lesions which were described as biliary cirrhosis of the liver. Mayer,[3] six years later, repeated their work and in the few animals that survived he found similar lesions. In 1873, Legg [4] reported the microscopic lesions found in the livers of cats following ligature of the common duct, and according to this worker, "the most important change is an increase in connective tissue which can be made out within a few hours, and which progressively increases destroying the tissue of the liver before it."

* Received for publication July 8, 1929.

In almost every succeeding year a paper has appeared dealing with this problem in pathology; however, reference will be made here only to those papers which discuss the histological changes as they are found in the liver of the guinea pig and other mammals.

Charcot and Gombault [5] in 1876 described three separate lesions; first, areas of necrosis; second, an increase in connective tissue confined largely to the interlobular areas; and lastly, an increase in bile ducts. Chambard,[6] a year later, verified these findings and in addition found mucous droplets within the cytoplasm of the liver cells and an interlobular increase in connective tissue, an observation later substantiated by Beloussow.[7] Litten [8] and Steinhaus [9] reported similar lesions except that they were unable to find an appreciable increase in connective tissue, whereas Bauer,[10] writing in 1882, considered the increase in connective tissue to be the outstanding feature. Lahousse,[11] differing from all earlier writers, found solely an increase in connective tissue without any change in the bile ducts.

Harley [12, 13] in 1898, and later in 1901, was one of the first to adopt an aseptic technique in the ligation of one hepatic duct in dogs and cats. He gave no bacteriological report but described a form of cirrhosis characterized by an interlobular fibrosis, a dilatation of the ducts and an atrophy of the liver cells.

Jagić,[14] Tischner,[15] and later Richardson [16] in 1911, and Rous and Larimore [17] in 1920 ligated the bile ducts of rabbits and found lesions essentially similar to those previously reported by Charcot and Gombault.

Ogata [18] took up a similar study in guinea pigs. He ligated the common duct in four animals; the first died in forty-eight hours with generalized peritonitis; the second, after the same length of time, showed no appreciable gross lesions; the third and fourth died suddenly on the fifth and eighteenth days respectively as a result of perforated gall bladders. His findings warrant a more detailed description although the possibility of infection and free bile in the peritoneal cavity must be considered as possible additional factors responsible for the histological lesions he described. After forty-eight hours obstruction he found typical areas of necrosis confined largely to the periphery of the lobules, scattered mitoses in the liver cells, and dilatation of the interlobular bile ducts. At the end of the fifth day, the areas of necrosis were bordered by encroaching

granulation tissue, the connective tissue had increased in the portal areas, and there was a new growth of bile ducts, of which only a few made connections with the liver cells. At the eighteenth day, the lobules were reduced to one-half their normal size by the increase in bile ducts and connective tissue. The new bile ducts were described as being very tortuous and irregular, and the many new sprouts extending out into the connective tissue resembled branches of a tree. At this later stage the necrotic areas were much less numerous.

Foà and Salvioli [19] in 1877 called attention to the fact that various experimental animals react differently following ligature of the common duct. This was an important observation for it must be considered in interpreting the apparently contrary conclusions arrived at by various workers using different animal species.

Ogata carried out a series of experiments similar to those performed in guinea pigs, using rats, rabbits, dogs, mice, pigeons and frogs, and found the usual necrotic areas in all animals except the dogs, frogs and mice; in the mice, however, the period of post-operative survival was but a few hours. There was a prominent and early increase in bile ducts in the rats and rabbits, whereas there was no such finding in either the pigeons, frogs or in a dog that lived but a week; however, the number of bile ducts was slightly increased in a dog that survived for thirty-five days. An increase in connective tissue was observed in all the animals which showed an increase in bile ducts.

From a review of this wide group of experiments it is apparent that as a result of prolonged bile stasis the liver does show definite changes that vary somewhat in different animals, both in respect to the histological findings and in the rapidity with which they are produced. However, in spite of the fact that almost identical lesions have been observed by many workers in different countries and at different times, there is no general agreement in either the interpretation or explanation of their findings.

Report of Experimental Work

Large healthy male guinea pigs were used because in these animals the lesions appear early, infection is infrequent, and the period of survival is sufficiently long to permit the changes becoming well advanced.

With the animals etherized, the peritoneal cavity was opened; the common duct was carefully isolated and ligated just at its entrance into the duodenum. The animals were afterwards kept separately and given their usual diet of greens, grain and water.

In an attempt to study the earliest changes in the liver, and to follow the lesions from day to day, the first animals to be examined were autopsied twelve hours after the operation, while others were autopsied every twenty-four hours thereafter for a period of twelve days. At the time of the autopsy, cultures were taken from the peritoneal cavity and liver and grown both aerobically and anaerobically. Moreover, only those animals were included in which there was no obvious infection, hemorrhage or free bile within the peritoneal cavity, and lastly, in which all cultures were sterile.

To obtain good fixation of tissue, the animals were bled at the time of the autopsy and pieces of tissue were placed immediately in formalin and in Zenker's solutions. The gall bladder in some of the animals was opened and the liver sectioned immediately; in others, the biliary system was preserved intact, in which case the portal vein was perfused with saline followed by Zenker's solution. In others, the portal vein was injected with India ink and the liver was preserved *in toto*, while in still others, a rather unsuccessful attempt was made to replace the bile and distend the biliary system with a suspension of ink in agar. To ensure that ligation had been complete, the duodenum was opened and pressure was applied to the gall bladder and common duct above the ligature, while an attempt was made to pass a small probe from the ampulla of Vater beyond the point of constriction.

Sections were embedded both in paraffin and in celloidin and stained with eosin and methylene blue and hematoxylin and eosin, while frozen sections of formalin-fixed material were stained with Sudan IV and Nile blue sulfate.

Pathological Report

This is based on a total of twenty "test" animals in which the period of survival after ligation of the common duct ranged from twelve hours to twelve days and is confined to an examination of the liver and extrahepatic biliary system.

The most outstanding lesion was the marked distention of the extrahepatic biliary system, which was observed as early as twelve

hours and found of even a greater degree in the animals that survived longest. In two of the animals which have not been included in the series, the gall bladder had ruptured, a finding not infrequently reported by former workers.

The liver becomes slightly enlarged in from twenty-four to forty-eight hours after ligation. At this time its surface is smooth and the capsule seems distended; later, after eight, ten and twelve days, the surface is very finely stippled, not unlike fine Morocco leather. The liver is bile-stained, but the color, unlike that caused by human bile, appears yellowish brown. Small, rather irregular, yellowish white areas, varying from 1 to 3 mm. in diameter are distributed beneath the capsule of the liver. At first there is no irregularity in the capsule over these anemic areas, but after several days the smooth capsular surface shows a very shallow pitting.

During the first few days there is no appreciable change in the consistence of the liver but later it becomes firmer and offers more resistance to cutting. When a liver is sectioned before fixation, watery yellow bile flows freely from the dilated ducts, the organ shrinks slightly and the ducts become partially collapsed. If, however, the liver is fixed before sectioning, the ducts and vessels remain distended even though the bile mostly escapes. When the portal vein was perfused with ink, the only portions of the liver that did not become discolored were the small scattered areas of necrosis.

Microscopic Report

Large Bile Ducts: The earliest and perhaps most important change to appear, and one that probably begins as soon as the common duct is ligated, is a gradual and progressive dilatation of both the extra- and intrahepatic biliary systems. With the gradual distention of the ducts, the epithelium at times becomes definitely flattened, and mitoses are quite numerous. Both the surrounding fibroblasts and liver cells show signs of this expansion; they are stretched, elongated and more compact than usual.

Areas of Necrosis: Great emphasis has always been given to large and small areas of necrosis that are commonly found in the periphery of the lobule. Because they occur very early and form rather outstanding histological lesions they are described here; however, they are of slight importance. In the twelve-hour guinea pig these

areas of necrosis are scattered throughout the entire parenchyma. They vary in size, some involving only a few cells, others an entire lobule. The liver cell is the first to show degenerative changes; later the endothelium lining the sinusoids; lastly, the reticulum framework, and when the lesion is centered about a small portal area the blood vessel is thrombosed, its wall necrotic, and even the small terminal bile duct epithelium may show both cytoplasmic and nuclear degeneration. A few of these areas contain scattered extravasated red blood cells, usually at the periphery. The most recent necrotic areas show no cellular reaction, a little later polymorphonuclear leucocytes are seen at the periphery, whereas after twenty-four to forty-eight hours the margin is infiltrated with both polymorphonuclear and endothelial leucocytes.

These areas of necrosis are formed largely within the first twenty-four hours after ligation; however, new areas do appear even up to twelve days. They do not seem to increase in size. On the contrary, those which are several days old are smaller, the adjacent liver cells have proliferated and a dense infiltration of endothelial leucocytes bordering the periphery have phagocytosed and removed much of the necrotic cellular débris.

Terminal Bile Ducts: The first change to occur in the bile ducts, apart from the simple dilatation, is a proliferation of the bile duct epithelium. This is shown by the presence of occasional mitoses as early as twenty-four hours. In forty-eight hours the bile ducts are already unusually prominent and mitoses are very numerous. On the third day bile is sufficiently concentrated in the distended ducts to become easily visible, and the bile duct epithelium shows still greater proliferation. With each successive day there is continued proliferation of the bile duct epithelium although after the tenth day mitoses are less numerous. With this great proliferation of the bile duct cells there is a marked elongation of preëxisting bile ducts with an apparent increase in their number. The terminal bile ducts of a normal guinea pig's liver are not always within the portal area; frequently they are seen traversing the peripheral zone of the lobule. This is important in interpreting the lesion sometimes seen in the peripheral zones during the later stages of biliary obstruction, because these apparent aberrant ducts, like the ducts lying within the portal areas, elongate, become tortuous, coiled and much more prominent. With this apparent increase, elongation and tortuosity

of the bile ducts, the portal areas are enlarged, they link up one with another dividing the liver parenchyma into separate and discrete lobules about two-thirds of the normal size.

Bile Capillaries: The bile capillaries lying between the liver cells are followed with difficulty during the first few days of obstruction, but later they become more clearly defined. A finding that is quite different from the picture seen in the human liver during biliary obstruction is the marked dilatation of that portion of the bile capillary adjacent to the portal area. In this area, the bile capillaries are distended into small cyst-like spaces with the bordering liver cells so flattened that it is difficult to distinguish them from proliferating bile duct epithelium.

Connective Tissue: The connective tissue in the portal areas is not appreciably increased until about the sixth day, although mitoses are found occasionally in fibroblasts as early as the third day. In the early stage this proliferation and increase in connective tissue is a relatively less prominent feature than the apparent increase in bile ducts, whereas later, in the ten and twelve-day animals, both bile ducts and connective tissue appear equally conspicuous. Moreover, resembling in distribution the dilated and elongated bile ducts, the connective tissue is confined to the interlobular areas.

The Liver Cells: As early as twelve hours the liver cells in the central and mid-zones are swollen, the cytoplasm is finely granular and contains small droplets of bile; later, hydropic degeneration of the liver cells is a more common finding and binucleate cells are frequent. Occasional individual cells scattered equally throughout different portions of the lobules show degeneration and necrosis. About the third day these necrotic cells become more plentiful and are seen more frequently adjacent to the portal areas and throughout the peripheral zone. Later these necrotic liver cells become less numerous and in the ten and twelve-day animals they are very infrequent. At the same time that one sees necrotic cells, other nearby cells show mitoses, a few as early as twenty-four hours, but after the second and third day, as many as one or two are seen in each oil immersion field. This proliferation of the liver cells decreases in the later stages so that in the twelve-day animals mitoses in the liver cells are practically absent.

The Kupffer Cells: Very early the endothelial cells lining the sinusoids are swollen and vacuolated. Some contain fat droplets, others

are distended with granules of hemosiderin. Mitoses are first seen in forty-eight hours; they become more numerous for a day or two and later almost disappear. With distention of the bile capillaries and swelling of the liver cells the capillary sinusoids are narrowed and often difficult to follow.

Cells in Portal Areas: An infiltration of cells into the portal areas appears in twenty-four hours and increases up to about the sixth or eighth day. Endothelial leucocytes are the first to appear; they proliferate rapidly and constitute the greater proportion of the free cells. Lymphocytes are less abundant, while scattered eosinophiles and occasional neutrophiles, though much less numerous, are seen in almost every portal area.

Blood Vessels: The portal veins, especially the medium-sized and larger vessels, become greatly distended. Usually the walls are quite normal, however small vessels with necrotic walls and lumina filled with fibrin thrombi are seen either in or bordering the areas of necrosis.

Lymphatics: In two of the test animals some of the larger lymphatics that drain the liver were included in the ligature of the common duct with the result that the lymphatics traversing the portal areas are extremely distended. Usually, however, these vessels are only slightly dilated and consequently much less conspicuous. Early, the portal connective tissue is unusually edematous but in the later stages this largely disappears.

Summary of Histological Findings

In reviewing the histological findings, it is apparent that as a result of biliary obstruction definite changes take place in the liver involving not only the large and small bile ducts but also the liver cells, the connective tissue stroma, capillary sinusoids and blood vessels. In the early stages the picture is characterized largely by the changes within the liver cells, the capillary bile stasis, the areas of necrosis and the cellular infiltration into the portal areas, whereas later it is dominated largely by the proliferation of bile duct epithelium, the elongation, tortuosity and apparent increase in bile ducts, and the increase in connective tissue in the portal areas. The end result is a rather uniform type of cirrhosis limited to the portal areas in which the lobules are diminished in size as a result of the expanding portal areas.

Discussion

Former workers have been unanimous in describing a proliferation and increase in the bile ducts, while Ogata even states that these new bile ducts frequently fail to make complete functional connections with the bile capillary system. Furthermore, in respect to the origin of these ducts Pick [20] believes that some arise from already existing bile ducts while others arise from the liver cells themselves. Gerhardt substantiates this view but Ogata could find no proof that liver cells could undergo such a transformation. From our studies we believe that the increase in bile ducts is simply an apparent change resulting from a proliferation of bile duct epithelium. In the livers that were fixed *in toto* with the bile ducts fully distended, we were able to follow the lumina of the elongated terminal bile ducts to their connections with the dilated lumina of the bile capillaries. Furthermore, India ink that was injected into the common duct could be followed through the tortuous terminal bile ducts into the bile capillaries.

Regarding the origin of the cells that form this apparent increase of bile ducts, we favor the opinion expressed by Ogata that they arise purely from a multiplication of preëxisting bile duct cells; however, in the later stages, when the liver cells lining the distended bile capillaries so nearly simulate bile duct epithelium it is almost impossible to differentiate the two types of cells and hence the embryonic or liver cell origin of bile duct epithelium cannot be denied positively.

The cause of the proliferation of the bile duct epithelium has also been a debated question, largely because of the misinterpretation of the existence of "new bile ducts." Chambard, Foà and Salvioli, Simmonds [21] and Pick explained the apparent increase in bile ducts simply as a concomitant phenomenon or as a sequence to the increase in connective tissue. Charcot and Gombault, and later Gerhardt, took the viewpoint that the bile duct proliferation was not merely a natural accompaniment to the connective tissue proliferation, but rather a separate and distinct process resulting from the increased pressure within the walls. However, Gerhardt also granted that an atypical growth of bile ducts could result from an increase in connective tissue. According to Ogata the bile duct and connective tissue proliferation are two quite unrelated processes re-

sulting from a thorough saturation with retained bile. It would appear, however, that since we are not dealing with a new formation of bile ducts but simply with an elongation of the connections that already exist, the presence of bile within the bile ducts would seem to be a sufficient and satisfying cause. Furthermore, the increase in connective tissue that is present in the portal areas has most likely been caused by a similar mechanical process of compression and stretching.

Much discussion has always arisen in regard to the origin of the areas of necrosis. Charcot and Gombault held the opinion that the pressure of retained bile ruptured the smaller bile ducts with the result that bile escaped into the lobules and killed the liver cells. Beloussow, Eppinger,[22] Abramow and Samoilowicz,[23] and Janowski,[24] from observations on human cases adopted a similar view. Foà and Salvioli found no rent in the bile ducts and thought that the increased pressure within the bile capillaries was sufficient to explain this necrotic process. Gerhardt, who also found no break in the biliary system, considered that the necrosis was the result of the chemical action of stagnant bile. Richardson and Ogata likewise considered that the injurious action of the bile was the cause of necrosis. Ogata, in attempting to explain the distribution of the necrotic areas, formulated the hypothesis that since all liver cells are not working at an equal rate at the same time and also because the outflow of bile in all capillaries is not equally rapid, then any sudden obstruction to the bile would result in a molecular destruction of the most actively functioning elements.

Tischner, years earlier when working with rabbits, felt that the degree of functional activity of the liver cells might play some part in determining whether or not they would undergo degeneration and necrosis, yet he considered it a relatively unimportant factor. He explained the lesions as simply areas of anemic necrosis resulting from obstruction to the circulation. The latter he estimated to be definitely decreased as a result of the increased pressure within the biliary system.

From our own observations we feel that the toxic effect of the bile, whether it reaches the liver cells by leakage or seepage, is of little importance. If it were extremely toxic the liver cells in the central zones that are filled with it from the onset would presumably be the first to undergo necrosis. These areas of necrosis resemble infarcts

in their appearance, contour and position, also in the type of inflammatory reaction that is limited to the periphery, and lastly in the manner of healing.

The effect of ligating the common duct is first to distend the bile ducts and produce a rise in pressure within the biliary system. Coincident and dependent on this is a probable decrease in the blood flow through the liver. Now, in addition to this general impairment in the hepatic circulation, there are the local changes which affect the terminal vessels. With distention of the bile ducts these smaller vessels may be collapsed entirely. This prevents the blood from flowing into the lobules and results in the formation of infarcts.

That these infarcts occur more commonly in the guinea pig and rabbit than in the dog and man is probably to be explained on an anatomical and physiological basis. The circulatory system is different; in man even the smallest portal areas contain both a branch of the hepatic artery and portal vein, whereas in the lower animals similar areas contain but a single, small, thin-walled vessel. This means that the most distal lobules are supplied with vessels that correspond to "end arteries." Furthermore, this implies that the connection between the hepatic artery and portal vein is not alone through a network of capillaries and sinusoids but also by larger communicating vessels, a fact which may be readily observed when India ink is injected into either the arterial or venous system.

The relation between the terminal vessels and bile ducts in guinea pigs is also rather unusual. They lie side by side, held together by a few strands of connective tissue which separate them from the surrounding liver cells. With such a close relationship and in such a restricted space, any distention of bile duct would of necessity encroach upon the vessel.

There is another point that is probably as important as either of these anatomical peculiarities and that is the amount of bile that is secreted by the different species of animals, for both the guinea pig and rabbit produce relatively many times as much bile as either dog or man.

Considering these three factors together, namely, the presence of "end arteries," the intimate relationship of vessels and bile ducts, and lastly the large quantity of bile secreted, it seems reasonable to assume that they would constitute a sufficient cause for the more frequent occurrence of infarcts in this group of lower mammals.

SUMMARY

Obstructive cirrhosis may be defined as a characteristic form of cirrhosis uniformly limited to all the portal areas throughout the liver. It is caused by an obstruction to the outflow of bile. In the early stages, bile stasis, necrosis and regeneration of individual liver cells, edema and infiltration of the portal areas are the most prominent features. Later there is an apparent increase in the number of bile ducts, the portal connective tissue is increased and with enlargement of the portal areas the liver becomes divided into small, separate and distinct lobules. In the guinea pig and rabbit, large and small areas of necrosis are early and constant findings.

Evidence is presented to show that the proliferation of bile duct epithelium results merely in an apparent increase in the number of bile ducts in the portal area and not in an absolute increase as has been described previously.

The proliferation of fibroblasts in the portal areas is interpreted on a mechanical rather than on a toxic basis.

The origin of the areas of necrosis is discussed, and the opinion is expressed that they are simply areas of infarction. Their relative frequency in lower mammals may be explained on an anatomical and physiological basis.

We are indebted to Dr. F. B. Mallory for his many suggestions and helpful criticism, and also for the photomicrographs. We also wish to thank Miss Marion E. Lamb and Miss Vida Randolph for technical assistance.

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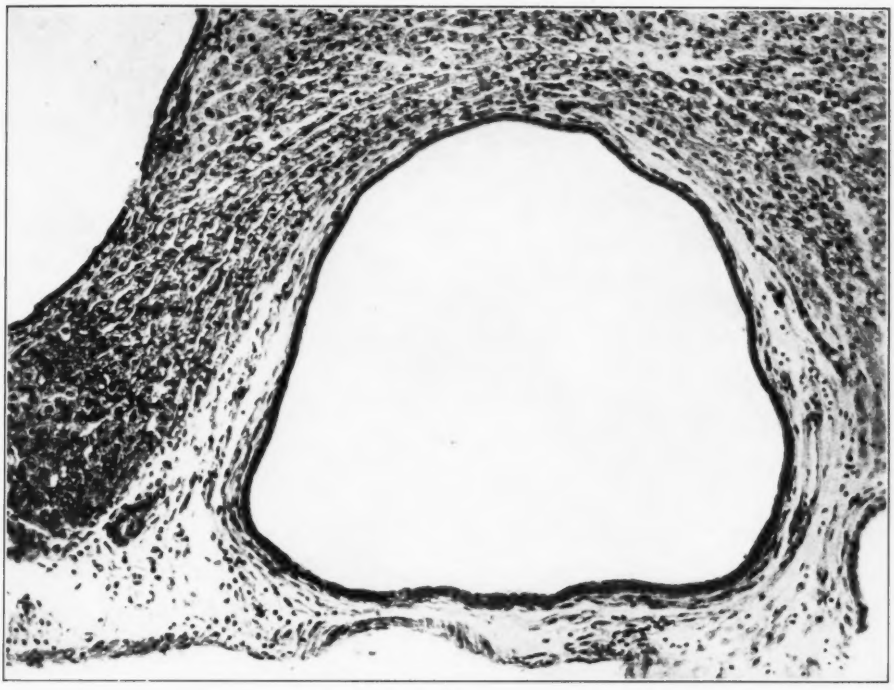
DESCRIPTION OF PLATES

PLATE 112

FIG. 1. Photomicrograph showing a medium-sized dilated bile duct. The adjoining connective tissue is stretched and compacted. The liver cells in the surrounding lobules are elongated, compressed and atrophic. There is a slight infiltration of endothelial leucocytes into the portal area. × 150.

FIG. 2. An area of infarction involving portions of three lobules centered about a single portal area. It is sharply demarcated from the surrounding liver tissue and infiltrated at the periphery with an inflammatory exudate composed of endothelial and polymorphonuclear leucocytes. × 150.



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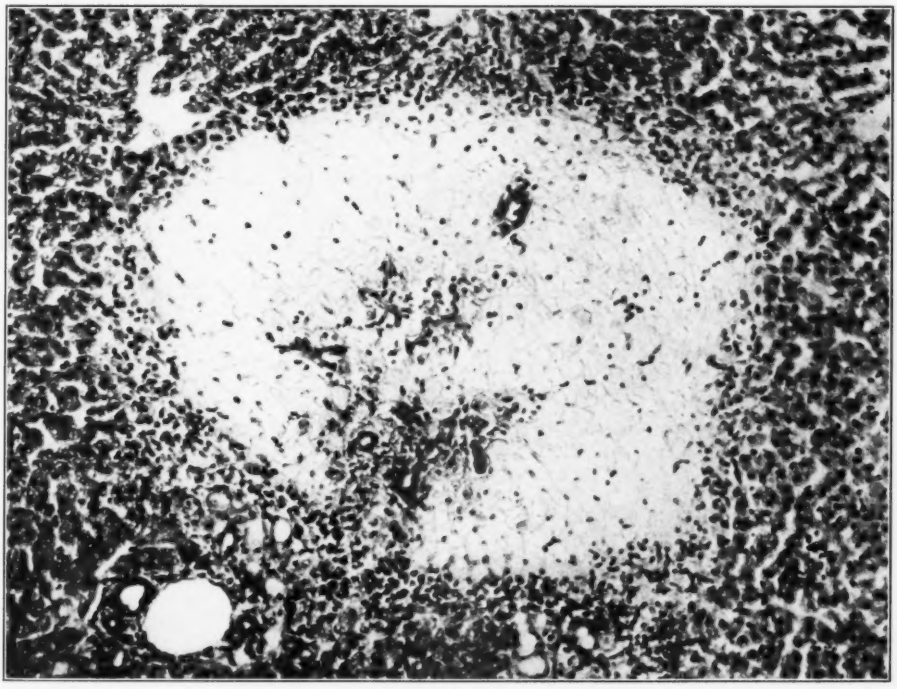

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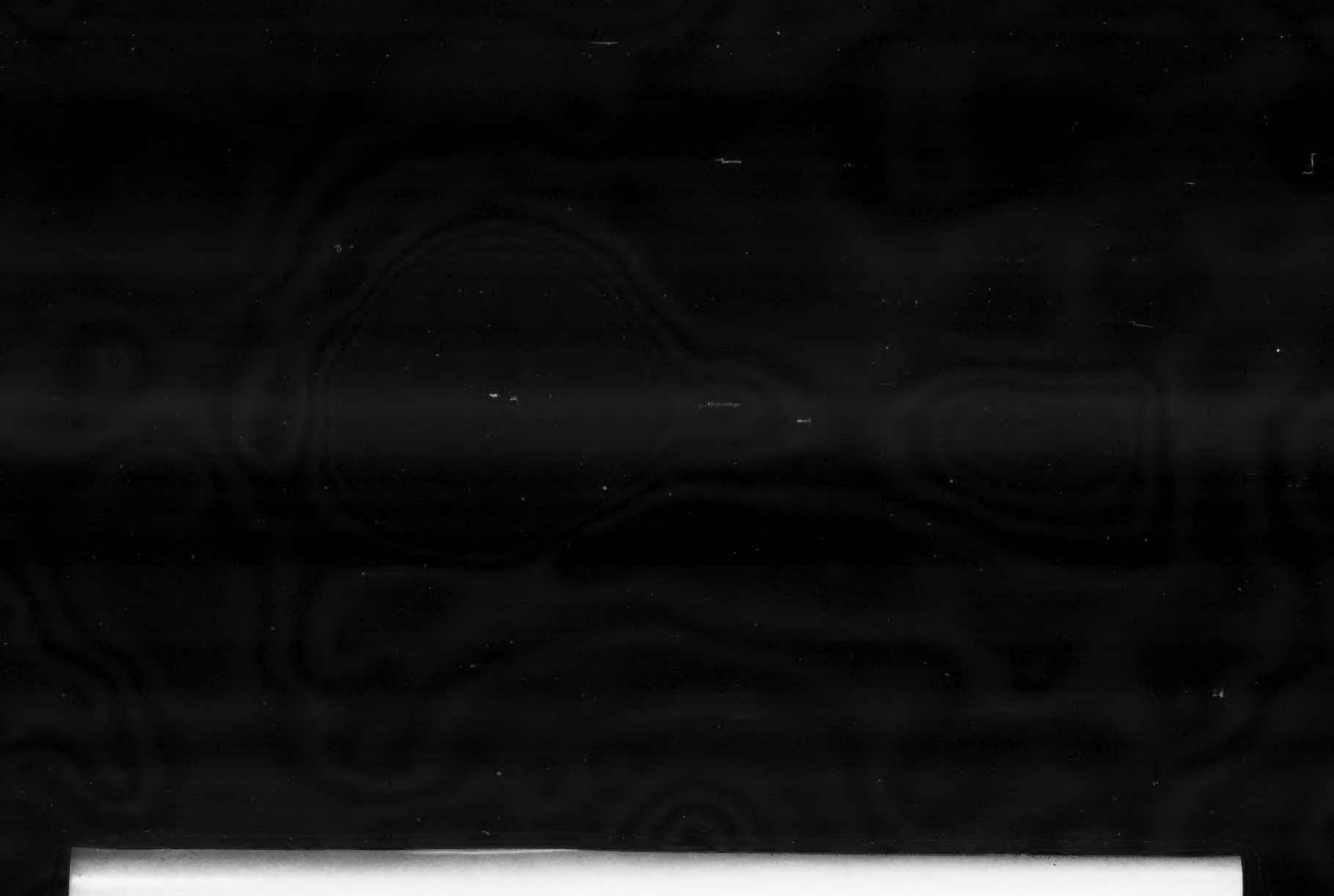
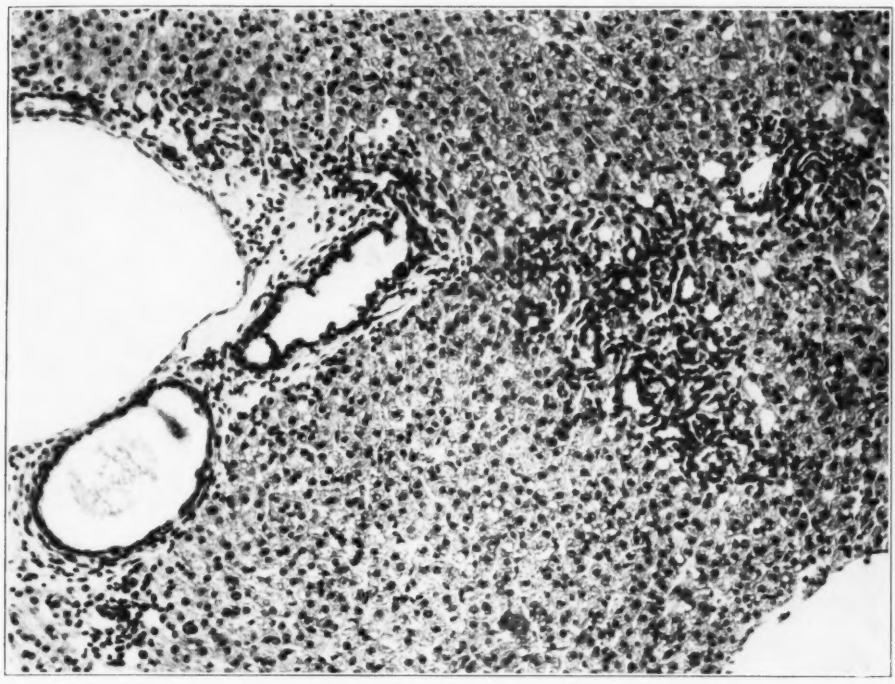
PLATE 113

FIG. 3. Photomicrograph showing distended medium-sized bile ducts and portal veins, a stretching and compression of portal connective tissue, and a slight infiltration by endothelial leucocytes. Toward the right is a smaller portal area characterized by an apparent increase in the small terminal bile ducts. × 150.

FIG. 4. A portal area in the liver of a guinea pig twelve days after ligation of the common duct showing true cirrhosis characterized by an apparent increase in the number of bile ducts and an increase in portal connective tissue. The bile capillaries in the peripheral zones of the surrounding lobules are distended into small cyst-like spaces. The liver cells surrounding the distended bile capillaries closely resemble the proliferating bile duct epithelium. Moderate infiltration of endothelial leucocytes and lymphocytes into the portal connective tissue. × 250.





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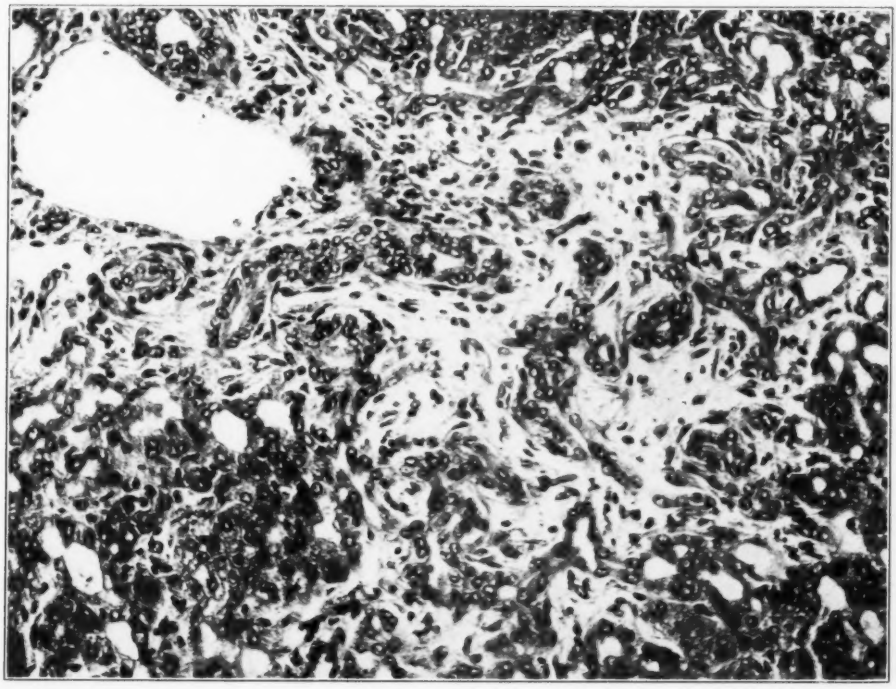

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OBSTRUCTIVE CIRRHOSIS *

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At the present time there is considerable confusion among both pathologists and clinicians in regard to the term "biliary cirrhosis." In its broader sense it is generally used to imply a form of cirrhosis confined fairly definitely to the portal areas and characterized by an increase in bile ducts and connective tissue. As regards etiology, biliary obstruction and infection are usually considered to be the important causative agents.

Several years ago Mallory [1] described an infectious type of cirrhosis resulting from bacterial infection of the smaller bile ducts. In contrast to this, the term "obstructive cirrhosis" is suggested to indicate that type which results purely from an obstruction to the outflow of bile. In either type it is clearly seen that we are dealing with a biliary form of cirrhosis in that it is the bile ducts that are primarily involved, and yet the two types are distinctly different both grossly and microscopically, and furthermore, either may be found quite independent of the other, although the two types are often combined.

The purpose of this paper is to describe briefly the gross and histological findings in obstructive cirrhosis, and to compare them with a similar form of cirrhosis which has been produced experimentally, in the absence of infection, in lower animals.

Literature

It is rather difficult to review the literature relative to this subject since little effort has been made to differentiate either the gross or histological findings of these two forms of biliary cirrhosis, namely, the obstructive and the infectious. Moreover, in infants, congenital malformations of the intrahepatic biliary system have at times not been recognized as such, and consequently have been occasionally included as forms of biliary cirrhosis of the liver.

Legg [2] in 1874 reported two cases of biliary cirrhosis, one in a

* Received for publication, July 8, 1929.

young woman who had been jaundiced but two weeks. A gall stone was found obstructing the common duct, and the liver showed microscopically a moderate degree of interlobular cirrhosis. The second case was an elderly male with a strong alcoholic history who had been jaundiced for nine months. The autopsy revealed hydatid cysts of the liver compressing the hepatic ducts, while microscopically the liver showed considerable "portal cirrhosis."

Charcot and Gombault [3] in 1876 reported four cases of biliary cirrhosis, one of which they described as infectious cholangitis. Mangelsdorf,[4] six years later, reported a much larger series of cases with brief postmortem findings and concluded that though the histological lesions varied greatly a fibrosis of the liver was the one constant finding. Janowski,[5] Ford,[6] Eppinger,[7] Abramow and Samoilowicz,[8] and Weber [9] have likewise reported and discussed numerous cases of biliary cirrhosis, but they have not attempted to differentiate the simple obstructive from the more complicated infectious lesions.

More recently Rous and Larimore [10] in 1920 made an effort to determine the effect that bile itself played in liver lesions. From their work, which was based on experimental studies in rabbits, they concluded that no human picture resembled even remotely the lesion that could be produced in these animals as a result of ligating the common duct. Furthermore, they pointed out that attempts to utilize such experimental work in the explanation of biliary cirrhosis in man had almost been given up.

On the other hand, Snell, Greene and Rowntree [11] were able to keep dogs alive for three months after ligation of the common duct and produced what they described as an experimental counterpart of the advanced biliary cirrhosis seen clinically in association with prolonged jaundice.

Judd and Counseller [12] have quite recently studied this problem again in human cases. According to these workers, when obstruction was due to cancer, occlusion of the common duct was more rapid and more complete and a condition of hydrohepatosis developed with little or no cirrhosis. If, on the other hand, obstruction was due to a stone or a benign stricture it was usually associated with a chronic infection, and such cases showed a marked portal fibrosis and a thickening of the ducts. Here again we are left in doubt as to just how much of the lesion in the latter cases could be

ascribed to simple obstruction and how much to the complicating infectious agent.

In infants who show cirrhosis of the liver in association with congenital malformations in the extrahepatic biliary system, we are confronted not only with the problem of obstruction and infection but also with the possibility of a congenital anomaly within the liver itself.

Legg [13] in 1876 was one of the first to draw attention to a form of cirrhosis associated with congenital absence of the common duct. Thomson [14] fifteen years later described the condition of congenital obliteration of the extrahepatic bile ducts and was able to collect forty-nine cases in which the liver showed an appreciable degree of cirrhosis. This number has since been almost doubled. Rolleston and Hayne,[15] Lavenson,[16] and Howard and Wolbach [17] have reported additional cases and described cases of their own. A case reported by the last two workers has been described in greater detail and warrants further consideration. A male child, when two weeks old, developed jaundice which progressed until his death four weeks later. The liver showed a more or less advanced cirrhosis of a mixed type with both central and portal sclerosis and a good deal of interlobular connective tissue as well.

In reviewing the many different lesions in children which have been ascribed to agenesis and atresia of the extrahepatic biliary system, we find that some workers have observed changes at the periphery of the lobule, others in the center, and still others have described a more diffuse process extending throughout the lobule. In addition, the possibility of infections, toxins and congenital intrahepatic anomalies has often been overlooked in their discussions.

Lastly, Rolleston [18] in summing up the many views regarding the production of cirrhosis solely from obstruction of the common duct concluded "that biliary obstruction *per se* does not constantly cause any form of cirrhosis."

I. Studies in the Infant

Etiology: In a group of ten cases that showed varying stages of simple uncomplicated obstructive cirrhosis six were caused by congenital atresia of the common duct, two by obstruction of the hepatic ducts, one as a result of an apparent absence of hepatic ducts,

and lastly, one in which the common duct was unusually elongated, kinked and distended with thick, colorless mucus.

Holmes [19] abstracted from the literature one hundred cases showing congenital obliteration of the bile ducts which indicates that this anomaly is not an extremely rare condition. Moreover, he pointed out that the obstruction may be single or multiple, may involve any portion of the ducts, and lastly, in at least sixteen of the cases surgical relief would have been possible.

Congenital absence of the common duct is a very much more uncommon finding. Kirmisson and Hébert [20] reported a case in which there was no trace of either hepatic, cystic or common duct, and were able to collect from the literature two cases similar to their own.

A few other examples of obstruction of the common duct which have been reported in infants were caused by the presence of large lymph nodes which pressed on the common or hepatic ducts.

In regard to the nature of atresia of portions of the extrahepatic biliary system, the most commonly accepted viewpoint, and one described by Beneke,[21] is that it is primarily a developmental anomaly. However, there are others who regard this condition as the healed stage of an acute cholangitis that occurred during fetal life, induced by maternal toxins and infections. Futhermore, there are those who believe that the cirrhotic changes in the liver are the result of an inflammatory reaction in that organ during fetal life, and that atresia of the ducts represents merely an extension of the process down into the larger bile passages.

We believe that the congenital atresia resembling congenital agenesia of the extrahepatic biliary system is primarily a developmental anomaly, that the cirrhotic changes in the liver are entirely secondary, and furthermore that the picture of uncomplicated obstructive cirrhosis is entirely different from the intrahepatic developmental anomalies involving either the bile ducts or the mesenchyma.

Gross Appearance of the Liver: In the early stages the liver, apart from a marked greenish discoloration, may appear quite normal. Even in the later stages the cirrhotic changes are relatively less conspicuous than in other forms of cirrhosis. The surface is uniformly covered with very fine granulations resembling fine Morocco leather. The liver is not increased in size, it is firm and cuts with increased resistance. In cases of very long standing the portal areas appear unusually accentuated on the freshly cut surface.

Microscopic Appearance of the Liver: The earliest cases in which we were able to see any changes other than the picture of simple bile stasis were in infants who had lived at least three weeks. Before this one finds bile within the liver cells, distending the bile capillaries, especially of the central zones, bile in the terminal and collecting bile ducts, and at times in the perisinusoidal spaces. The liver cells may be rather swollen, may vary somewhat in size and contain two or more nuclei, but mitoses are infrequent. The Kupffer cells are unusually conspicuous, apparently increased in size and number, and may contain droplets of inspissated bile. But with all this, there is no appreciable change within the portal areas except a slight infiltration by endothelial leucocytes, a few of which may contain blood pigment and bile.

The beginning of the cirrhotic process is characterized by an apparent increase in the terminal bile ducts. The bile duct epithelium proliferates as shown by the presence of mitoses and the ducts become lengthened and tortuous, but no new bile ducts are formed. This process is going on in every portal area throughout the liver so that one finds this change bordering the larger portal areas as well as in the smaller. Moreover, since the effects of the obstruction are equally distributed throughout the terminal bile ducts, any changes that they may undergo are carried out in a uniform manner throughout the liver. At the periphery of the lobule the bile capillaries are frequently so distended that they compress the bordering liver cells, and in following the lumina of the bile capillaries into the terminal bile ducts it is practically impossible to determine where liver cells stop and bile duct epithelium begins.

Accompanying this elongation of terminal bile ducts there is a gradual proliferation of fibroblasts in the portal areas so that more and more connective tissue is formed in the portal areas as the process progresses.

The whole process is so gradual that the circulation has an opportunity to adjust itself to these changes so that infarcts, which are invariably found in animals in which the common duct has been suddenly ligated, are extremely uncommon.

In the later stages, the portal areas are uniformly increased in size throughout the liver, partly as a result of the apparent increase in bile ducts due to elongation of them, and partly owing to an absolute increase in the amount of connective tissue. Along with this

change, the lobules have diminished somewhat in size, although even in those cases which had lasted three to four months we found neither central sclerosis nor an appreciable increase in the interlobular connective tissue.

Clinical and Pathological Aspects: One of the most variable findings in an infant's liver is the amount of bile in liver cells and bile capillaries. Kölliker [22] found that the secretion of bile begins as early as the third month of embryonic life; however, it is probable that this would be delayed considerably and diminished in cases of atresia. Furthermore, the degree of blood destruction varies considerably in this group of infants, a condition which, as pointed out by Rous and Drury,[23] largely regulates the quantity of pigment in the bile.

In our small series of ten cases, jaundice had been present since birth; however, there are innumerable cases reported in which jaundice did not appear for days or weeks later. According to Porter,[24] "jaundice is the predominant symptom and while it may be present at birth, its appearance is sometimes delayed until toward the end of the first month." In cases of complete congenital atresia, this delayed appearance of jaundice is difficult to understand.

Various gross changes have been reported in the liver and other organs. Many authors have described both liver and spleen as being greatly enlarged, while others have found fibrosis in the pancreas. In our small series the liver was of normal size; no constant changes were seen in the pancreas, nor was there any evidence of portal obstruction as characterized by an enlarged spleen, varices or ascites.

A clinical summary of our cases shows that jaundice, hemorrhages, pigmentation of the urine and clay-colored stools were the outstanding features. Nutrition in most cases was well maintained for some time in spite of the severity of the lesion, but later the health inevitably gave way and the child rapidly lost weight and strength. The longest surviving case that we encountered lived for four and a half months; however, reports of six to eight months' survivals are not uncommon in the literature, while two cases are said to have lived nine months, one until the eleventh, and one reported by Porter, as long as the fourteenth.

II. Studies in the Adult

Etiology: Of twenty cases of obstructive cirrhosis in adults that came to autopsy, eight resulted from tumors about the head of the pancreas and ampulla of Vater, eight from stones in the common duct, and four from benign strictures. Of this series only five of the cases were females and it is interesting to note that in each of these cases the obstruction was due to stones. The average age of the males was about 55 years and of the females about 60, although in both groups there was a wide variation.

Gross Appearance of the Liver: The liver was normal in size and contour, and the surface was quite smooth except in those cases of long standing when it was uniformly and very finely granular. The consistence also varied somewhat, but only in the later stages had it appreciably increased, and then it was never so marked as in long standing cases of alcoholic, pigment, toxic or infectious cirrhosis. In all of the cases except one the whole organ was deeply bile-stained; the one case which was an exception had been caused by a stone that was removed a month or two before the patient came to autopsy.

Microscopic Appearance of the Liver: This differs slightly in adults and children, and in the former, seldom if ever, becomes such a conspicuous feature as one finds in the long standing cases in infants. Furthermore, in elderly patients, where obstruction has existed for many weeks, atrophy and degeneration of the parenchyma gradually become a more prominent part of the picture. In addition to these minor variations that are associated with the age of the individual, one occasionally finds a combination of two or more types of cirrhosis, such as obstructive and infectious, or obstructive with an alcoholic or pigment cirrhosis, and in such cases either the gross or histological picture may become extremely complicated.

In the early period of biliary obstruction the pathology is simply that of bile stasis, as was the case in both infants and animals, but in adults the picture is more clearly defined, and one has a better opportunity to study the changes in the bile, in the liver cells, in bile ducts and in the connective tissue stroma.

Bürker [25] has divided the lobule of the liver into two parts, namely a central portion for secreting and a peripheral portion for absorbing, and such an hypothesis would seem to be substantiated, at

least in part, in cases of bile stasis. A few days after biliary obstruction, while bile is still being actively secreted, the liver cells in the central zones show more or less regressive changes. The cells are irregular in size and shape, the cytoplasm may stain quite intensely or appear unusually pale, in a few cells it may scarcely stain at all, while here and there one sees a necrotic bile-stained cell that is being invaded by endothelial leucocytes. The nuclei also vary in size, contour and in the arrangement of the chromatin; and liver cells with three, four and five nuclei are not at all uncommon, while occasionally, though rarely, mitoses are also found. The bile that lies in the cytoplasm of the liver cells sometimes appears as yellowish and green granules; at other times as large and small droplets. It may be clumped in a small focus bordering the nucleus, it may form a complete halo about the nucleus, and lastly it is sometimes diffusely scattered throughout the cell. Bile that is homogeneous and orange to greenish, distends the bile capillaries but can seldom be traced into the lateral canaliculi between the liver cells. The Kupffer cells, especially those in the central zones, are increased in number, swollen and contain bile in the form of granules and droplets. The inspissated masses of bile in the dilated bile capillaries appear cylindrical, irregular and branching and vary from orange to dark green. They are often extruded and lie between the liver cells and the walls of the sinusoids. Here they are phagocytosed by endothelial leucocytes which in consequence may become greatly enlarged and occasionally multinucleated. The leucocytes sometimes accumulate in considerable numbers and necessarily compress the sinusoids. The result is that the picture in the centers of the lobules is often complicated because of the difficulty of distinguishing the endothelial cells lining the sinusoids from the endothelial leucocytes attracted out of the circulation. Endothelial leucocytes containing granules and droplets of bile are often present also in the lymphatics and stroma of the periportal tissue.

A little later, though the liver cells may still show retrograde changes, and be swollen and vacuolated, they contain less bile, which usually lies clumped about the nucleus. Here and there one finds bile in both liver cells and Kupffer cells throughout the lobule, but this is not common and in such cases the quantity of bile in the periphery is much less than in the centers of the lobules. At this stage the number of bile-stained endothelial leucocytes may be in-

creased in the portal areas, but usually there is no apparent change in either the bile ducts or portal connective tissue.

The earliest structural changes to become manifest were found in two cases in which the common duct had been completely blocked by large biliary calculi for a period of three weeks. In all the portal areas the terminal bile ducts were unusually prominent, they were filled with bile and showed an apparent increase in number, while associated with this change was a slight increase in portal connective tissue.

We have followed the progressive histological changes in both bile ducts and connective tissue in cases in which complete obstruction has existed for as long as eighteen months, in a second group of cases in which obstruction has been incomplete for an equal length of time, and lastly in a group in which obstruction has been intermittent over a period of three to five years.

The changes in all cases have been much the same, the difference lies only in degree. The bile duct epithelium of both collecting and terminal ducts proliferates, and there is a progressive elongation of the periportal bile ducts which become tortuous and much more conspicuous. The portal connective tissue is increased and in it one finds an infiltration by endothelial leucocytes, lymphocytes, scattered eosinophiles and basophiles. If the obstructing agent, such as a stone, has been removed some time before death, bile stasis will probably be absent, and the elongated bile ducts in the portal areas are much less conspicuous.

In brief, then, the picture that one usually finds in an uncomplicated case of biliary obstruction of several weeks duration is characterized by an increase in size of the portal areas due to an elongation of the terminal bile ducts, a proliferation of connective tissue, and an infiltration by both endothelial leucocytes and lymphocytes. The liver cells in the central zones show mildly regressive changes and inspissated bile fills the bile capillaries.

However, other changes occur with sufficient regularity to warrant further consideration. In six of the twenty livers which have been included in this series there were infarcts which varied in number, in size and in the stage of resolution. They usually involved only a portion of a lobule and in all cases radiated out in a fan-like manner from the portal areas. Furthermore, they appeared in cases where the obstruction had occurred quite suddenly and had been

quite complete. These infarcts, when first formed, resemble those that are constantly found in the livers of lower animals following experimental common duct ligation;[26] there was little extravasated blood, slight peripheral reaction and no discoloration with bile. Later there is phagocytosis of this necrotic tissue by encroaching endothelial leucocytes and finally even these cells disappear leaving a rather loose structureless area of connective tissue.

Another lesion that sometimes may be quite confusing in long standing cases is the cellular reaction to old inspissated bile that lies free in the portal connective tissue. Apparently as the result of pressure, the epithelium lining the small ducts may become greatly stretched and finally disappear leaving a large tubular mass of inspissated bile surrounded by connective tissue. The bile acts simply as a foreign body, such as agar, and is soon attacked by endothelial leucocytes and foreign body giant cells, while still later fibroblasts proliferate about it and traverse it giving it the appearance of an old, partially organized thrombus.

In two cases in which obstruction had been present about six weeks there was a small irregular accumulation of bile in the connective tissue of two or three of the medium-sized portal areas suggesting that there had been a rupture of one of the smaller bile ducts. There was a zone about this, infiltrated with a few polymorphonuclear and endothelial leucocytes, but there was no necrosis of the liver cells in the surrounding lobule.

A change in the portal vessels was a very uncommon finding and occurred in only one of our cases. As a result of a benign stricture of inflammatory origin about the lower end of the common duct there had been complete obstruction to the outflow of bile for more than a year. In this case there was a very marked subintimal proliferation of connective tissue in the medium-sized branches of the portal vein, which considerably narrowed the lumen. Moreover, this was the only uncomplicated case of obstructive cirrhosis showing ascites. It is well recognized that as a result of bile stasis the pressure within the portal circulation is increased, and presumably if other cases had progressed for longer periods of time a secondary sclerosis of the vessels would not have been such an unusual finding.

In two cases of long standing biliary obstruction, both in elderly people, there were small scattered foci, most numerous in the central zones, in which the liver cells had disappeared leaving the trabecu-

lar spaces filled with fatty and pigmented endothelial leucocytes. A similar observation was described by Ogata [27] who attributed it to the presence of retained bile within the liver cells of the secreting portion of the lobule. However, though degenerative changes as well as occasional necrotic cells were frequently seen within the central zones, larger areas from which the liver cells had entirely disappeared were very much rarer and should probably be explained as due not alone to the action of the bile but also to the impairment of the liver circulation and lack of regenerative activity on the part of the remaining cells.

In reviewing these more unusual changes that are sometimes found, it is apparent that a well marked case of obstructive cirrhosis in an adult may show not only a dilatation and elongation of bile ducts and an increase in the portal connective tissue, a variable degree of bile stasis and retrograde changes in the centers of the lobules, but also infarcts, organizing bile thrombi, evidence of ruptured bile ducts, sclerosed vessels and small irregular foci in which the liver cells have disappeared.

Clinical and Pathological Aspects: Jaundice that was intense, enduring and unassociated with signs of sepsis, was present in all cases. However, the duration of life after the onset of jaundice varied greatly not only in cases due to different causes but also in different cases resulting from a similar cause; thus in cases of obstruction due to tumors and gall stones it ranged from three weeks to six months averaging in all about two months, while in three of the cases associated with gall stones there was in addition a history of intermittent jaundice for two, three and five years. In cases due to stricture, of which we have included but four, jaundice was present for two, three, eight and eighteen months respectively.

The patients generally had fairly good health at first, but toward the end of life, gastro-intestinal disturbances, loss of weight and strength were almost constant findings.

The liver was normal in size, and only in long standing cases showed appreciable gross evidence of cirrhosis. Furthermore, there were no outspoken signs of portal embarrassment such as enlargement of the spleen, ascites, hematemesis or varices, except in one patient who lived eighteen months after the onset of jaundice. These are rather important points because they assist in the differential diagnosis of this form of cirrhosis.

COMMENT

Comparatively little attempt has been made in the diagnosis of the various forms of cirrhosis to differentiate as a distinct and characteristic type that form which is found in prolonged and uncomplicated obstruction to the common bile duct. One reason for this has probably been its relative lack of importance, but another and more obvious reason is that it has been loosely crowded into that rather heterogenous group labeled "biliary cirrhosis," or included among those in which there has been a terminal bile duct infection.

It would appear that obstructive cirrhosis in childhood is not materially different from the lesion one finds in the adult, and it is precisely the same in principle as one finds in the lower animals subjected to ligation of the common duct.

In the study of autopsy and surgical material from human cases both in children and adults we have had an opportunity to follow each stage in the development of this form of cirrhosis. In the lower animals, such as the guinea pig, changes occur with great rapidity, and it would also appear that in the infant, cirrhosis develops more quickly than in the adult, at least it becomes very much more conspicuous in a similar period of time. The early stage in all cases is characterized by a dilatation of the ducts, with bile stasis within the lobule. This is followed by an elongation of the terminal ducts associated with an appreciable increase in portal connective tissue, commonly accompanied with a moderate cellular infiltration into the portal areas and the appearance of regressive changes in the liver cells in the central zones of the lobule.

With biliary obstruction there is an impairment in the hepatic circulation, although only very rarely are there visible signs of interference with the portal circulation.

SUMMARY

1. This paper is based on the study of thirty cases of uncomplicated obstructive cirrhosis, ten in infants and twenty in adults averaging about sixty years of age.

2. The common cause in infancy is a congenital malformation of the bile duct, whereas in the adult it results from tumors, concretions and inflammatory strictures.

3. The gross and microscopic findings of obstructive cirrhosis are described, and in addition, reference is made to a few of its more important clinical features.

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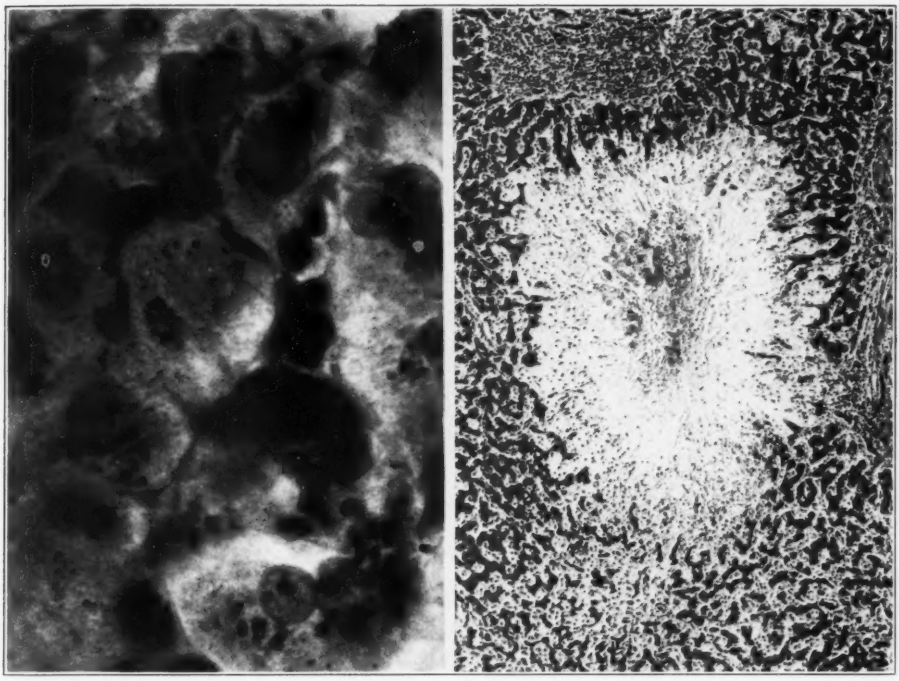
DESCRIPTION OF PLATES

PLATE 114

FIG. 1. OS 29.18. Section of a bit of liver tissue removed from a man 40 years of age who was operated on for acute obstruction of the common bile duct. Recovery was complete. The liver cells are enlarged and contain numerous granules and droplets of bile. In a dilated bile duct is a branching mass of inspissated bile. × 1000.

FIG. 2. 23.44. Obstructive cirrhosis secondary to cicatricial contraction around the ampulla of Vater in a man 75 years of age. Jaundice for two months. The photomicrograph shows an infarct with beginning organization at the periphery. × 80.

FIG. 3. M 1074. Female infant 28 days old. Congenital obstructive cirrhosis. A portal area showing increase of connective tissue and a number of bile ducts. × 100.



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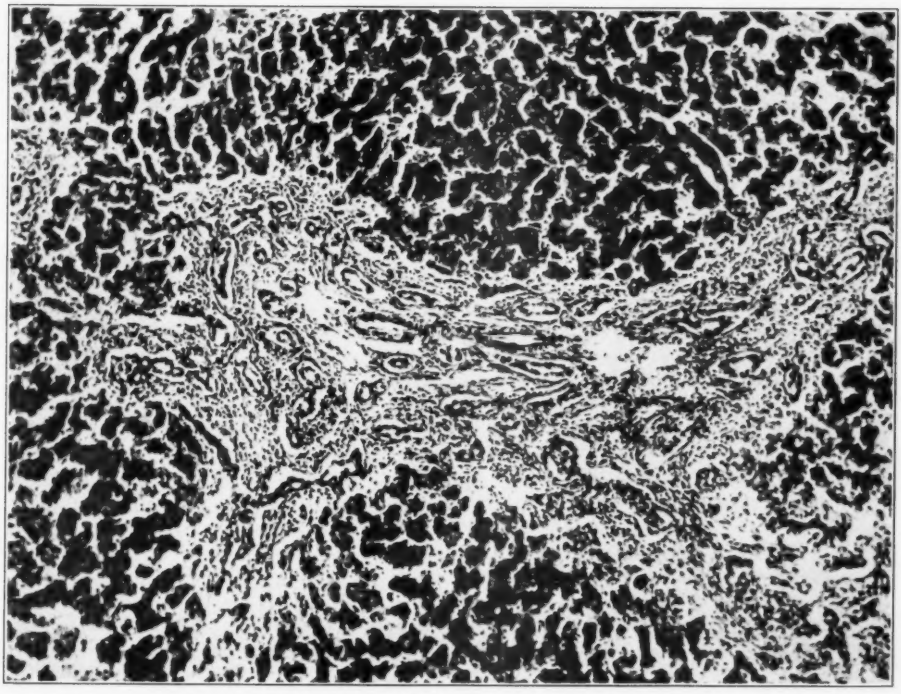


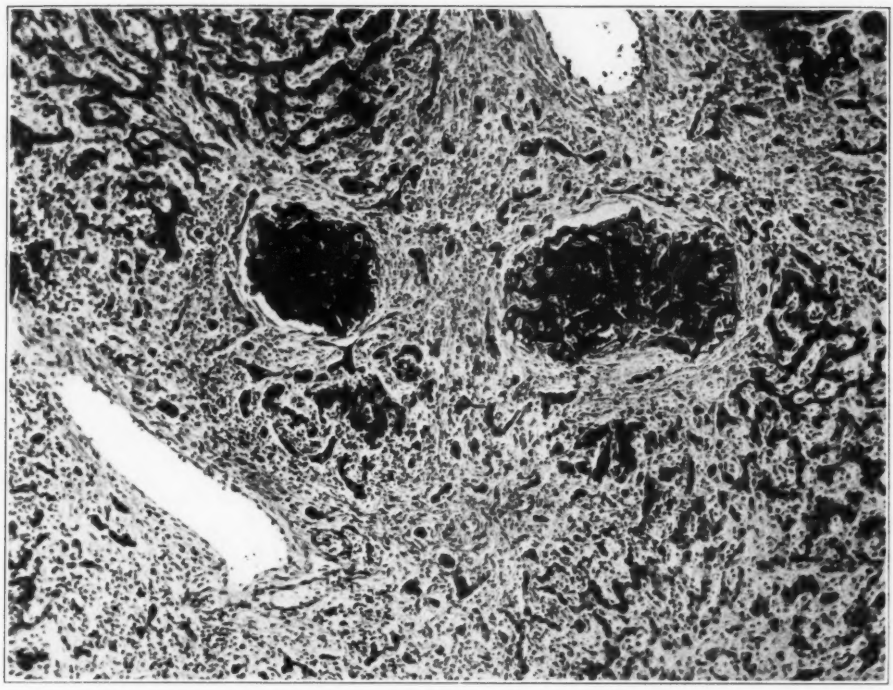
3

MacMahon and Mallory Obstructive Cirrhosis

Plate 115

Fig. 4. 22.298. Obstructive cirrhosis of considerable duration in a man 54 years of age. Two masses of old inspissated bile in bile ducts are undergoing organization. The periportal connective tissue is greatly increased in amount and has numerous bile ducts included in it. × 100.

Fig. 5. M. 1074. From same liver as shown in Fig. 3. A mass of inspissated bile in a bile duct surrounded and infiltrated by endothelial leucocytes and foreign body giant cells. × 500.



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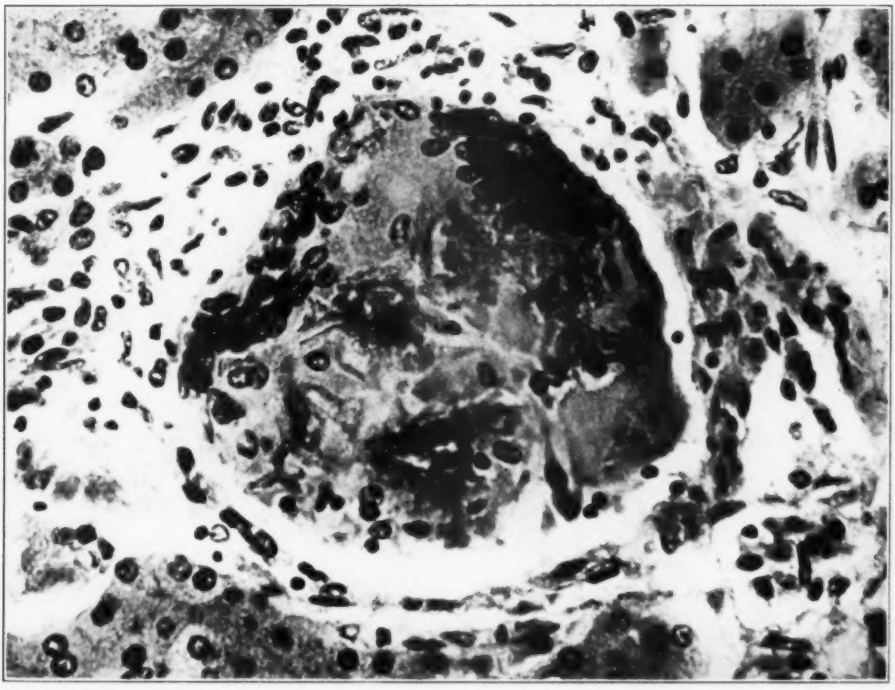

5

MacMahon and Mallory Obstructive Cirrhosis

STUDY OF A MENINGIOMA IN SUPRAVITAL PREPARATIONS, TISSUE CULTURE AND PARAFFIN SECTIONS *

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Tissue cultures of intracranial tumors removed at operation in this clinic have been successful for certain of the gliomas, such as the glioblastoma multiforme and the medulloblastomas. Outgrowths of cells have been observed in some of the thirty-one meningiomas cultured during the past two years but as Kredel [1, 2] has previously stated, the growing cells seemed to be of the mononuclear macrophage series and not tumor cells. From their phagocytic properties and growth pattern, the cells were considered to be clasmatocytes which were seen abundantly in the supravital preparations of the meningiomas.

Recently a rapidly growing meningioma was removed at operation and portions of the tumor were studied in immediate supravital preparations, in tissue cultures of the same bits of tissue, and in stained paraffin sections. The cells growing out in culture in a pattern like that of cells of mesodermal origin, closely resembled the tumor cells seen in the supravital preparations and in the paraffin sections. Phagocytic cells were not observed among the growing cells. The growing cells did not appear to be of the fibroblastic type and in the stained sections of the fixed tissue the cells had no resemblance to fibroblasts.

This single instance of a successful tissue culture of a meningioma is presented because it shows by the growth pattern the mesodermal origin of the cells of this tumor, that the tumor cells had no demonstrable phagocytic powers, and that the real phagocytic elements were clasmatocytes which are so commonly found in human and animal tumors.

Parasagittal Meningioma Localized by Ventriculography. Extirpation. Recovery

Clinical History: Case P.B.B.H. Surgical No. 33356. On February 23, 1929, William M. was referred by Dr. Howard F. Root of Boston, with a diagnosis of tumor of the brain. For three years before admission the patient was known

* Received for publication July 31, 1929.

to have had diabetes mellitus in a mild form and was treated accordingly. Because of an exacerbation of this illness he was admitted to the Deaconess Hospital for observation. While there he complained of diminution in vision, suboccipital headaches and unsteadiness in gait which had been present for the preceding two months. The ophthalmological examination showed a bilateral choking of the optic discs and the patient was transferred to this hospital.

The admission examination showed a papilledema of 1.5 diopters on the right and 2.5 diopters on the left. The visual fields were constricted to tubular vision in each eye. There was suboccipital tenderness and stiffness of the neck. Signs of a subtentorial lesion were found in the hypotonia of the upper extremities and adiadokocinesia of the left side. The roentgen-ray examinations of the skull and chest were considered normal.

Course of Illness: On the day after admission the previously demonstrated signs of a cerebellar lesion were less distinct and in view of the increasing papilledema and absence of localizing symptoms a right subtemporal decompression was made on March 12, 1929. This procedure gave but temporary relief and as the intracranial pressure increased ventriculography was made nine days later. From the deformity of the ventricles a right frontal tumor was suggested and a right osteoplastic intracranial exploration was made and a large vascular parasagittal meningioma was removed by Dr. Cushing. The operation was a long and difficult one as was the postoperative course.

At present, June 26, 1929, the patient reports as perfectly normal and at work.

The observations on the supravital preparations, tissue cultures and paraffin sections are given in the order in which they are routinely made for the intracranial tumors removed in this clinic.

Supravital Studies: Preparations of the fresh tumor with neutral red dye solution were made immediately at operation. Examination showed a densely cellular tissue. The cells were connected one to another, forming narrow columns which were typical of the general architecture of the tumor (Fig. 1*a*). The cell bodies were oval or polyhedral with a delicately granular cytoplasm nicely defined, except in areas so crowded with cells that only the nuclei could be clearly distinguished. There was no evidence of cellular division. The nuclei were oval or round, containing fine chromatin particles and one or more nucleoli (Fig. 1*b*). A few strands of collagen were present (Fig. 1*d*).

Most conspicuous in the preparation were the extraordinary numbers of clasmatocytes scattered among the tumor cells or arranged in clumps. During the period of observation they became packed with neutral red dye inclusions which varied from very fine granules to vacuoles huge in size (Fig. 1*c*).

Tissue Culture Studies: Numerous tissue culture preparations were made by the hanging-drop method. Tissue adjacent to that

used for supravital preparations was used. In each of thirty separate cultures there was seen extension of cells from the explant into the culture media. The cells were all of the same type and grew out in a reticular pattern as do cells of mesodermal origin (Figs. 2 and 3). In eight of the cultures the growth was profuse, the cells extending to the periphery of the growing space in four days.

The first evidence of growth was seen five hours after the cultures were planted when single cells, with oval bodies and long processes connected to the explant, jutted out into the media. The cells grew out evenly and were always connected with each other by processes extending from one cell body to another. This gave a reticular pattern to the growth. No mitoses or direct cell divisions were seen. The cell bodies varied in shape and were usually oval or triangular. Changes in the shape of the cell bodies were seen only at the periphery of the growth. No motile cells and no cells resembling clasmatocytes were seen among the growing cells although such cells were recognized in the explants.

The phagocytic powers of the cells of the culture were tested by adding red blood corpuscles of the patient and of other patients, as well as carmine particles to the culture media. There was no evidence of phagocytosis among the cells although the materials remained in the culture media for four days in several preparations.

The cultures were fixed in 1 per cent formalin and in formalin ammonium bromide and stained successfully with hematoxylin and eosin and unsuccessfully by Cajal's gold chloride sublimate method.

Pathological Studies: The tumor weighed about 115 gm. The overlying dura and bone were roughened, thickened and involved by the encapsulated tumor which resembled other meningiomas seen in this clinic.

Microscopic Studies: The paraffin sections were stained with eosin-methylene blue, phosphotungstic acid hematoxylin and by Perdrau's method for connective tissue. The tumor is densely cellular, moderately vascular and sharply marked off from the small portions of compressed cerebral tissue attached to the specimen (Fig. 4). The cells are closely packed together and are often arranged in short or long strands or cords (Fig. 5). There is neither whorl formation, calcification nor evidence of degeneration in the material studied.

The cells are similar and are oval or polyhedral with oval or

rounded nuclei and a moderate amount of cytoplasm. Each nucleus contains one or several nucleoli and occasionally mitoses are seen. The individual cells show no evidence of laying down specific substances. The small amount of collagen present is usually near blood vessels. The stroma is scanty and phagocytic cells are not recognized. The cell type and arrangement are similar to those seen in sections of several recurrent and atypical meningiomas.

To summarize, the cells of this tumor as seen in supravital preparations, in growing tissue cultures, and in paraffin sections appeared to be of the same type. Clasmatocytes were seen in the supravital preparations and in the explants, but were not recognized in the paraffin sections.

It is our opinion that the cells which grew out in culture in a reticular pattern, typical of cells of mesodermal origin, were tumor cells.

Comment

It is known that in the tissue culture of animal tumors, either sarcoma or carcinoma, different types of cells grow out. Certain of these cells were recognized by Lambert and Hanes [3] as stroma cells which were distinct from the tumor cells in their pattern of growth. They also found that the stroma cells were actively phagocytic and ingested carmine particles.

Lewis and Gey [4] described as clasmatocytes the cells called stroma cells by Lambert and Hanes, and found that they were present both in the supravital preparations and the tissue cultures of mouse sarcoma.

That there has been some question as to whether scavengers, macrophages or clasmatocytes so frequently found in animal tumors are malignant cells or not is evidenced by the work of Fell and Andrews.[5] From their studies made by the hanging-drop method, these investigators were unable to tell which of the two cell types found in cultures of Jensen's rat sarcoma was the malignant cell.

Carrell and Ebeling [6, 7, 8] answered this problem, for by their most refined tissue culture methods they were able to isolate the fibroblastic and the macrophage cells and to prove that the former cell was the real tumor cell of the Jensen's rat sarcoma. They also found that pure cultures of animal tumor cells may be grown *in vitro* but *in vivo* the tumor cells need the macrophages or clasmatocytes for their growth. Furthermore they showed that in tissue cultures pure

cultures of animal tumor cells attracted clasmatocytes. Finally it was their opinion that clasmatocytes stimulated the proliferation of fibroblasts and tumor cells in tissue culture, probably playing a rôle in the nutrition of growing cells by aiding in the furnishing of food to these cells.

In the many immediate supravital preparations made from portions of intracranial tumors removed by Dr. Cushing, clasmatocytes were commonly observed especially in the smears from the rapidly growing gliomas and meningiomas. The clasmatocytes may be considered as a normal constituent of these tumors *in vivo*, as they are so considered in certain animal tumors.

In the reports of his investigations of the tissue cultures of intracranial tumors removed in this clinic, Kredel [2] stated that in six of nine meningiomas there were outgrowths of cells which seemed to be of the mononuclear macrophage series which were proved to be actively phagocytic and most probably clasmatocytes. He further stated that the cells growing out from the explants of meningiomas did not grow in the reticular pattern as do fibroblasts nor did they behave as do fibroblasts in the presence of arsenious trioxide.

Tissue cultures have been made of twenty-two meningiomas presenting a histological structure similar to that of the other meningiomas cultured. In twenty-one of these tumors there was an abundance of collagen, psammoma bodies and cellular whorls; certainly not the type of a tumor from which a growth of tumor cells in tissue culture could be expected. In but one instance, that of the case herein reported, has there been an outgrowth of cells which could be considered as tumor cells, although cells regarded as clasmatocytes were observed.

As stated, the tumor of the case presented was considered to be a meningioma from its gross appearance and from the histological study of both the paraffin sections and the supravital preparations. In the tissue cultures there was an abundant growth of similar cells always in the form of a reticular pattern. These cells resembled the cells of the tumor as seen in the supravital preparations. They were found not to have phagocytic properties. They were considered to be the tumor cells of the meningioma, and of mesodermal origin as their pattern of growth was like that of cells of mesodermal origin. They did not resemble cells which are fibroblastic in origin, for no substances were seen to be laid down by the cells.

Summary and Conclusions

1. The tumor cells of a meningioma were found to be similar in type and arrangement in supravital preparations, tissue cultures and paraffin sections.

2. Two types of cells were recognized in the supravital preparations, one the tumor cell and the other a macrophage or clasmatocyte. The latter type of cell seems to be essential for the continued growth of animal tumor cells *in vitro* and probably *in vivo*.

3. In tissue cultures the tumor cells of the meningioma grew in a reticular pattern as do cells of mesodermal origin and were not found to have phagocytic powers. It would seem that the phagocytic cells seen in meningiomas are clasmatocytes and not tumor cells.

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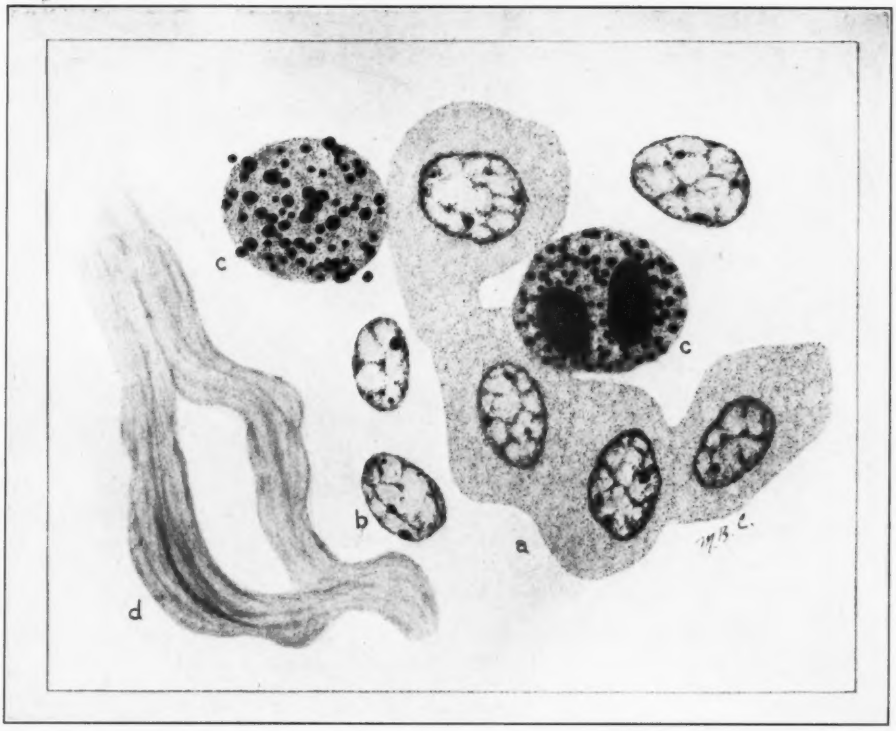
DESCRIPTION OF PLATES

Plate 116

Fig. 1. Drawing from original sketch from supravital preparation showing: (*a*) a typical column of tumor cells; (*b*) the vesicular nuclei; (*c*) clasmatocytes filled with neutral red dye inclusions; (*d*) strands of collagen.

Fig. 2. Showing the reticular outgrowth of cells from the explant (*A*) typical of mesodermal tissue and the grouping of some cells in small cords as seen in all of the cultures. The fixation in Zenker's fluid and the subsequent staining in hematoxylin and eosin have necessarily altered the cells. × 300.

Fig. 3. Showing an area of Fig. 4 under higher magnification to illustrate the reticular pattern of growth and the grouping and connections of cells.



1

2

Buckley and Eisenhardt

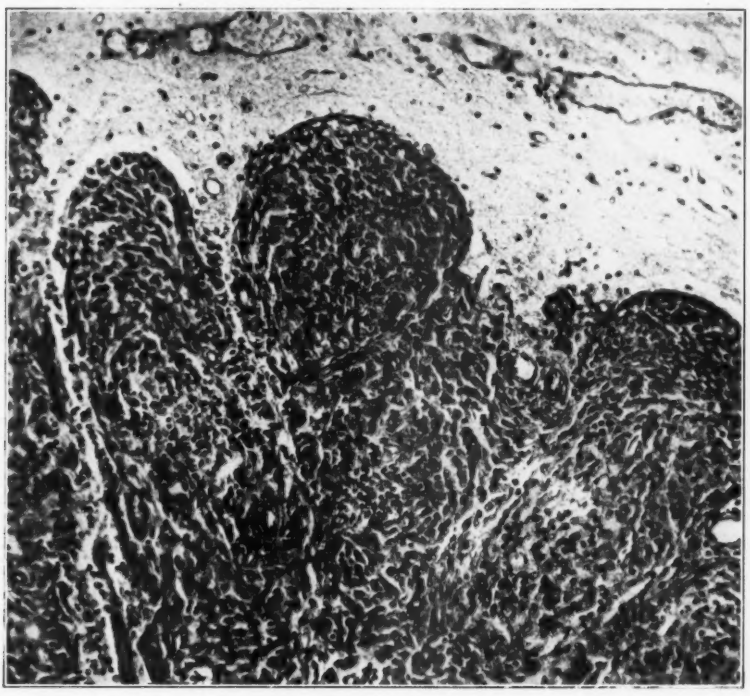
3

Study of a Meningioma

PLATE 117

FIG. 4. Section taken from the edge of the meningioma to show the sharp demarcation between tumor and compressed but uninvaded brain tissue. Hematoxylin and eosin. × 150.

FIG. 5. Showing the tendency of the cells to grow in narrow cords. Hematoxylin and eosin. × 600.



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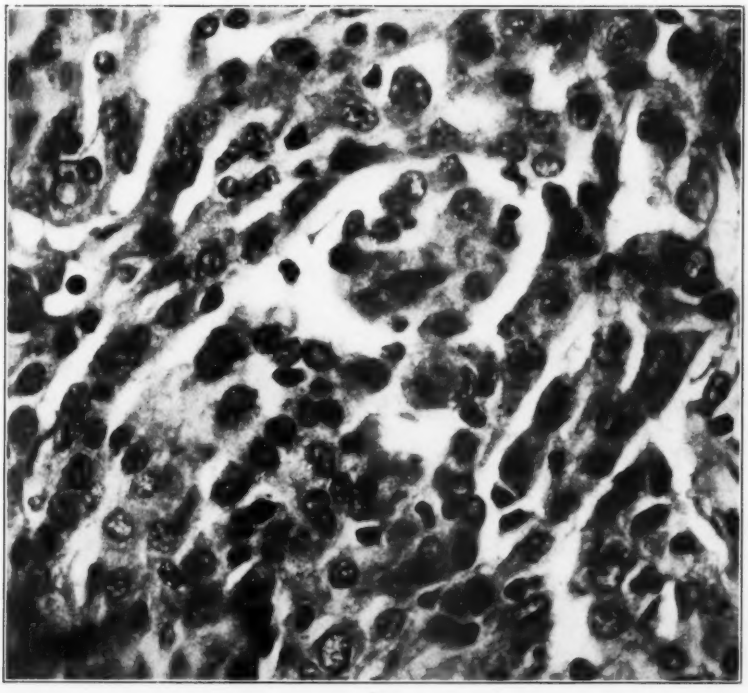

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